Mesenchymal Stem Cells Repair Retinal Vasculature in Retinopathy of Prematurity Mouse Model

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Introduction: Retinopathy of prematurity (ROP) is the leading cause of visual impairment and blindness in premature infants. ROP is a biphasic disease: 1) upon exposure of preterm babies to high O2 levels compared to those in utero, a process of retinal vasoobliteration (VO) takes place. 2) As a result of ensuing tissue ischemia, exaggerated neovascularization (NV) occurs notably caused by excessive secretion of vascular endothelial growth factor (VEGF). Consequently, the superficial retinal blood vessels abnormally penetrate into the vitreous causing retinal detachment and vision loss. The current ROP treatments, including laser photocoagulation and anti-VEGF intravitreal injections, only tackle aberrant vessel growth without repopulating the avascular regions of the retina. Thus there is a dire need of new therapies fostering normal retinal vascularization while arresting pathologic NV. Because stem cells have been found to enhance revascularization following ischemic insults, we surmised that they can accelerate normal retinal revascularization and in turn prevent aberrant intravitreal NV.

Methods: A well-established mouse model of oxygen-induced retinopathy (OIR) which replicates both phases of ROP was used herein. Briefly, at postnatal day 7 (P7) mice are subjected to 75% O2 until P12 to induce VO followed by room air leading to NV. Bone-derived Mesenchymal Stem cells (MSCs) are isolated from adult mice and then injected intravitreally either at the onset of VO (P7) or NV (P12) to assess prevention or repair of vascular damage respectively. VO areas were analyzed subsequently at P12 and P17. Moreover, migration of MSCs in OIR retinas was traced following injection. To determine the direct effect of MSCs on endothelial cell growth, aortic ring assay was performed in conjunction with MSCs co-culture in normoxic and hypoxic environments. Gene expression analysis by quantitative PCR was performed on OIR retinas injected with MSCs to determine possible factor(s) involved in revascularization. Factors investigated are VEGF, IL-1β and Sema3A known to drive NV, whereas IGF-1, Netrin-1 and Sema3E reduce NV.

Results: MSCs injected in OIR retinas (1) significantly reduced VO areas and inhibited formation of neovascular tufts, (2) migrated to the avascular regions and (3) localized adjacent to endothelial cells. In aortic ring assay, MSCs had no effect on the sprouting of endothelial cells in normoxia; however in hypoxia, MSCs restored endothelial cell growth initially curbed by low oxygen levels. Furthermore, MSC-injected OIR retinas showed an augmented expression of IGF-1, VEGF, Netrin-1, and Sema3E, and decreased expression of IL-1β and Sema3A; collectively diminishing NV.

Conclusion: MSCs can (1) arrest NV while inducing revascularization in the avascular areas of OIR retinas and (2) mediate vascular repair in a paracrine fashion by regulating the expression of growth factors, inflammatory cytokines and guidance cues.

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