

AB042. microRNA-96-based therapy protect microvasculature against oxygen-induced retinopathy: a novel uncovered property of miR-96 in vascular repair

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Background: Ischemic retinopathies (IRs) are ocular disorders associated to microvascular degeneration leading to visual impairments and blindness. microRNA (miRNAs) are a family of non-coding RNAs that regulate a wide range of gene expression involved in various biological process such blood vessel development and pathological NV. However, the post-transcriptional modulation of miRs and especially, their specific functions in the eyes during IRs remain to be evaluated. We aim to evaluate the potential role of miR-96 on microvascular degeneration in a rat model of oxygen-induced retinopathy (OIR).

Methods: *In vivo*: next generation sequencing (NSG) was used to perform a complete miRNAs profiling in the retina and choroid from OIR and normoxia (CTL) rats. To evaluate the effects of miR-96 on microvasculature, OIR animals were treated with a miR-96 mimic (1 mg/kg) or a control-miR by intravitreal injection before hyperoxia-exposure (80% O₂). Immunostaining analysis of retinal flatmounts and cryosections was used to explore the microvascular

effects of miR-96. *In vitro*: Human Retinal Microvascular Endothelial Cells (HRMVEC) were subjected or not to hyperoxia (80% O₂) and transfected with 50 nM of miR-96 mimic or antagomir-96. Angiogenic assay was performed (tube formation and migration) and molecular analysis evaluated by qRT-PCR and western blot.

Results: NSG and qRT-PCR analyses identified miR-96 as one of most highly expressed miRNAs in retina and choroid during development. However, miR-96 showed a strong downregulation in OIR rats, and also in HRMVEC subjected to hyperoxia. In HRMVEC, we found that miR-96 regulates positively the expression of the key pro-angiogenic factors VEGF, FGF-2 and ANG-2. To better explore the role of miR-96 on HRMVEC angiogenic activity, we performed a gain/loss of function study. Similarly, to hyperoxia exposure, we observed a robust angiogenic impairment (tube formation and migration) on HRMVEC transfected with an antagomiR-96. Interestingly, overexpression of miR-96 completely recued the basal phenotype of HRMVEC and protected against hyperoxia-induced endothelial dysfunction. *In vivo*, intravitreal injection of miR-96 mimic (1 mg/kg) in OIR rats significantly restored retinal vascular density and choroidal tightness/sprouting ability. This was accompanied by the restoration in the physiological levels of VEGF, FGF-2 and ANG-2.

Conclusions: This is the first study showing that reduced expression of miR-96 in OIR conditions lead to a reduction of VEGF/FGF/ANG-2 signaling, and inefficient post-ischemic revascularization in retinal/choroidal tissues. Intravitreal supplementation of miR-96 using a miR mimic could constitute a novel therapeutic strategy to improve vascular repair in IRs.

Keywords: Ischemic retinopathy; miRNA; angiogenesis; vascular repair; hyperoxia

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