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Mitochondrial Transplantation as a Novel Inducer of Retinal Pigment Epithelium Epithelial-Mesenchymal-Transition and Fibrosis

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Age-related macular degeneration (AMD) is the leading cause of loss of vision of aging populations in developed countries worldwide. Late-stage progression of AMD is characterized by subretinal fibrosis driven by epithelial-mesenchymal-transition (EMT). During EMT, the retinal pigment epithelium (RPE) - the primary support tissue for photoreceptors – lose their epithelialization and transition into a mesenchymal phenotype. This alteration leads to loss of tight-junction proteins, such as E-cadherin, and increased invasiveness of the cells, ultimately resulting in geographic atrophy of the RPE and overlying retina. Further, it is well-reported that production of metalloproteinases in late-stage AMD induces fibrosis causing irreversible vision loss. Recently, mitochondrial transfer has emerged as a critical component in disease pathogenesis such as AMD. Though EMT and fibrosis in AMD has been well-characterized, the role of isolated mitochondria transferred between RPE has never been explored. Here, we characterize the role of isolated mitochondrial transfer as a novel mechanism of metabolic crosstalk and disease induction in the RPE tissue. Cytokine induced-diseased mitochondria were isolated from RPE cells treated with AMD-associated cytokine TGF β 2 (10 ng/mL), administered to recipient RPE cells and the effects of Mito_{TGF β 2} were compared to control Mito_{Ctrl}, purified from healthy, untreated RPE, or positive control directly treated TGF β 2. We showed that treatment of healthy RPE with Mito_{TGF β 2}, and not Mito_{Ctrl} induces disruption of the mitochondrial network, reminiscent of the direct effect of TGF β 2 treatment. ELISA assay validated no direct TGF β 2 treatment was carried into the purified mitochondrial fraction. Both assessment of genetic profile via qPCR and bioenergetics via Seahorse XFe96 bioanalyzer validated the ability of Mito_{TGF β 2} to mirror the effects of TGF β 2-induced EMT and fibrosis through suppression of mitochondrial respiration and upregulation of fibronectin 1 (FN1). Our results elucidated that mitochondrial transfer induces a context-specific phenocopy that recapitulates the phenotype of donor to host RPE cells. This novel model of disease pathogenesis in RPE may provide insight to the presently nebulous centrifugal expansion of geographic atrophy of RPE in AMD and may provide promising insights to the development of therapeutics for EMT and fibrosis-driven disorders such as in late-stage AMD.