From Brain to Eye: Repurposing Dimethyl Fumarate to Target Vascular Endothelial Growth Factor-Induced Angiogenesis in Retinal Endothelial Cells

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Introduction: Vascular endothelial growth factor (VEGF) plays a role in blood vessel growth during embryogenesis and wound healing but a pathological role in wet age-related macular degeneration (nAMD). Endothelial cells primarily rely on glycolysis for metabolism, but switch to oxidative phosphorylation (OXPHOS) during angiogenesis. Dimethyl fumarate (DMFu), an FDA-approved oral tablet for multiple sclerosis, has shown anti-angiogenic properties in psoriatic models. Here we explore the ocular context using mouse choroidal explants and human microvascular retinal endothelial cells (HRECs). **Methods:** 1mm^2 choroid/RPE explants from 3-wk-old C57BL/6J mice were embedded in Cultrex and treated with 80μM DMFu. Scratch wound assays were performed on serum starved HRECs treated with 10ng/mL VEGF +/- 80μM DMFu to assess cell migration. Similarly treated HRECs were seeded on Cultrex-coated plates for tube formation and analyzed using the ImageJ Angiogenesis Analyzer. Treated HRECs were RNA sequenced and differentially expressed genes were identified. Pathway enrichment was assessed through over-representation and gene set enrichment analysis (GSEA), and unbiased weighted correlation network analysis (WGCNA). Protein expression of electron transport chain complexes was assessed by western blot and a Seahorse XFe96 Analyzer was used to quantify OXPHOS and glycolysis. **Results:** DMFu reduced choroidal explant sprouting area by 88.65% compared to control (n=4, $p<0.05$); HREC migration and tube formation were also significantly disrupted. GSEA revealed downregulation of VEGF-induced and VEGF-independent proliferation associated pathways with DMFu, including kinesin superfamily protein genes—affecting organelle and chromosome motility during segregation. WGCNA identified a link between tube formation and mitochondrial translation in DMFu groups compared to control. Complex II protein expression decreased by 65.35% (n=3, $p<0.05$) and a concurrent increase in glycolysis was observed with DMFu-treated HRECs through lower maximal OXPHOS and increased glycolytic capacity on Seahorse. **Conclusions:** DMFu exhibited potent anti-angiogenic properties in HRECs and mouse choroidal explants, indicating a promising avenue as an oral therapeutic for nAMD. Mechanistically, DMFu reduced complex II protein and OXPHOS with concomitant increased glycolysis leading to perturbations in microtubule formation and chromosome segregation. Future studies will examine its efficacy in nAMD *in vivo* models.