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The Roles of Lower Glycolytic Enzymes and Transporters in Regulating the Integrity of Retinal Vascular Endothelial Cell Barrier

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The Roles of Lower Glycolytic Enzymes and Transporters in Regulating the Integrity of Retinal Vascular Endothelial Cell Barrier

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Purpose: Damage to the retinal endothelial cells (RECs) is implicated in the progression of retinal degenerative diseases, including diabetic retinopathy and diabetic macular edema. While the role of glycolysis in glucose homeostasis is well-established, its contribution to REC barrier assembly remains unclear. In this study we investigated the importance of lower glycolytic components in maintaining the barrier integrity of human RECs (HRECs).

Methods: Electric cell-substrate impedance sensing (ECIS) technology was employed to analyze the real-time impact of various glycolytic enzymes and transporters on the maintenance of HREC barrier integrity, represented by resistance (R) across the cells. Heptelidic acid was used to inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH); NG52 to inhibit phosphoglycerate kinase 1 (PGK1); AP-III-a4 to inhibit enolase; shikonin to inhibit pyruvate kinase M2 (PKM2); galloflavin to inhibit lactate dehydrogenase (LDH); AZD3965 to inhibit monocarboxylate transporter 1 (MCT1); and MSDC-0160 to inhibit mitochondrial pyruvate carrier (MPC). Concentrations of 1 µM and 10 µM were tested for each inhibitor. The viability of the HRECs was evaluated using an LDH cytotoxicity assay at 24 and 48 hours.

Results: R across the HRECs was most significantly decreased with PKM2 inhibition with shikonin and GAPDH inhibition using heptelidic acid, which was not due to reduced cellular viability. Interestingly, inhibition of PGK1 with NG52 had a protective effect on HREC barrier integrity.

Conclusions: This study highlights the critical role of PKM2 and GAPDH...
in maintaining the barrier integrity of HRECs. Understanding the contributions of each glycolytic component to the HREC barrier facilitates the development of targeted interventions to treat retinal endothelial cell dysfunction.