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Relative Importance of Different Mitochondrial Components in Maintaining the Barrier Integrity of Retinal Endothelial Cells: Implications for Vascular-associated Retinal Diseases

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Abstract : Purpose: Mitochondria dysfunction is central to breaking the barrier integrity of retinal endothelial cells (RECs) in various blinding eye diseases such as diabetic retinopathy and retinopathy of prematurity. Therefore, we aimed to dissect the role of different mitochondrial components, specifically, those of oxidative phosphorylation (OxPhos), in maintaining the barrier function of RECs. Methods: Electric cell-substrate impedance sensing (ECIS) technology was used to assess in real-time the role of different mitochondrial components in the total impedance (Z) of human RECs (HRECs) and its components; the capacitance (C) and the total resistance (R). HRECs were treated with specific mitochondrial inhibitors that target different steps in OxPhos: Rotenone for complex I; Oligomycin for ATP synthase; and FCCP for uncoupling OxPhos. Furthermore, data were modeled to investigate the effects of these inhibitors on the three parameters that govern the total resistance of cells: cell-cell interactions (Rb), cell-matrix interactions (α), and cell membrane permeability (Cm). Results: Rotenone (1 µM) produced the greatest reduction in the Z, followed by FCCP (1 µM), whereas no reduction in the Z was observed after the treatment with Oligomycin (1 µM). Following this further, we deconvoluted the effect of these inhibitors on Rb, α, and Cm. Firstly, rotenone (1 µM) completely abolished the resistance contribution of Rb, as the Rb became zero immediately after the treatment. Secondly, FCCP (1 µM) eliminated the resistance contribution of Rb only after 2.5 hours and increased Cm without considerable effect on α. Lastly, Oligomycin had the lowest impact among these inhibitors on Rb, which became similar to the control group at the end of the experiment without noticeable effects on Cm or α. Conclusion: These results demonstrate differential roles for complex I, complex V, and coupling of OxPhos in maintaining the barrier functionality of HRECs, in which complex I being the most important component in regulating the barrier functionality and the spreading behavior of HRECs. Such differences can be used in investigating gene expression as well as for screening selective agents that improve the functionality of complex I to be used in the therapeutic approach for treating REC-related retinal diseases.

Keywords : human retinal endothelial cells (hrecs), rotenone, oligomycin, fccp, oxidative phosphorylation, oxphos, capacitance, impedance, ecis modeling, rb resistance, α resistance, and barrier integrity
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