TRPV4 activation reduces transepithelial resistance of retinal pigment epithelial cells

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Purpose
Retinal pigment epithelium plays an essential role as part of the blood retinal barrier. Disruption of this barrier function has been linked with multiple ocular diseases. Thus, understanding mechanisms involved in its regulation is important. The role of TRPV4 activation, which reportedly disrupts tight junctions of several cell types including retinal endothelial cells, in modulating RPE barrier function was examined in this study.

Methods
First passage porcine RPE cells were cultured on transwell inserts for weeks to allow differentiation. Transepithelial electrical resistance was measured using Epithelial Volt Ohm Meter (EVOM), and cells with TEER higher than 400 ohm cm2 were used for experiments. QRT-PCR was utilized to examine mRNA expression, and immunocytochemical staining was performed to examine protein localization. TRPV4 activity was modified via specific agonist GSK1016790A and antagonist HC-067047.

Results
QRT-PCR confirmed TRPV4 mRNA expression, and TRPV4 protein was primarily localized at the apical cell-cell border in differentiated RPE cells. TRPV4 specific agonist GSK1016790A dose-dependently reduced TEER, with significant reduction observed at 1nM and higher. This effect was blocked in the presence of selective TRPV4 antagonist HC-067047, confirming the role on TRPV4 in the process. In agreement with the TRPV4 localization, application of the agonist to the apical surface had significantly faster effect to reduce TEER compared to basolateral application. Intracellular calcium buffering using BAPTA-AM had little effect on TEER reduction by GSK1016790A, suggesting a localized reaction not affected by global buffering.

Conclusions

Activation of TRPV4, localized on the apical surface, leads to reduced TEER in differentiated RPE cells. TRPV4 may play a role in ocular diseases with disrupted RPE barrier function, and therefore, further studies are warranted.