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Mechanosensitive TRPV4 Channel is Involved in Fibrotic Transdifferentiation of Retinal Pigment Epithelial Cells

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Sustained presence of myofibroblasts during wound healing can cause fibrosis. Within the eye, transdifferentiation of retinal pigment epithelial (RPE) cells to myofibroblasts have been implicated as a key event leading to fibrotic scarring of the retina. While TGF-beta signaling has been shown to play key roles in this process, inhibition of this pathway can result in undesirable side-effects by preventing physiological function of this multifaceted cytokine. Therefore, identification of other pathways/molecules that could potentially be targeted to prevent fibrotic scarring is warranted. In this study, roles of mechanosensitive channel TRPV4, which has been implicated to play roles in several fibrotic diseases, and its downstream effector MLCK in myofibroblast transdifferentiation of RPE cells as well as matrix contraction, a key phenomenon of retinal scarring, were examined.

Primary cultured porcine RPE cells were used to assess matrix contraction. Cells were cultured with media containing TGF-beta on collagen matrices in the presence or absence of TRPV4 inhibitor HC-067047 or MLCK inhibitor ML-7. Collagen matrices with attached cells were released from 24 well plates and contraction was assessed as change in size of matrices. Cells on these matrices were then lysed to examine the expression of myofibroblast marker protein tropomyosin 1 (TPM1) as well as TRPV4 by western blot analyses.

TGF-beta treatment significantly increased collagen matrix contraction by cultured RPE cells compared to untreated controls. TGF-beta treatment did not significantly affect TRPV4 expression. Inhibitors for TRPV4 and MLCK significantly reduced matrix contraction as well as TPM1 expression. These data implicate that TRPV4 signaling pathway, while not directly regulated by TGF-beta, is involved in myofibroblast transdifferentiation of RPE cells and subsequent fibrotic contraction of the matrix.

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