論 文 要 旨

TNF-α disrupts morphologic and functional barrier properties of polarized retinal pigment epithelium

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Retinal pigment epithelial (RPE) cells form a blood-ocular barrier, and their polarized property is crucial for maintaining their barrier functions. Tumor necrosis factor alpha (TNF-α), a major pleotropic inflammatory cytokine that causes disruption of barrier function and eventual angiogenesis, is expressed in the choroidal neovascularizations of age-related macular degeneration eyes. Thus, it most likely plays an important role in the progression of the disease. The purpose of this study was to compare the effects of TNF-α on the barrier function of polarized RPE cells. Nonpolarized RPE cells were used as negative controls. Isolated porcine RPE cells were seeded on TranswellTM membranes. The polarization of the RPE cells was determined by their high transepithelial electrical resistance (TER >150 Ω*cm2) and by their differential secretion of vascular endothelial growth factor (lower layer/upper layer >2.5X). Polarized RPE cells were incubated with 10 ng/ml of TNF-α and the TER was measured. TNF-α significantly decreased the TER of polarized RPE cells by 17.6 ± 2.7% ($P<0.001$) of the control at 24 hours and that of non-polarized RPE cells by 5.4±6.5% ($P=0.401$). The p38 mitogen-activated protein kinase (MAPK) inhibitor, SB203580, blocked the effects of TNF-α of decreasing the TER. Cell junction-related molecules, e.g., ZO-1, located between cells in control RPE cells, were disassembled by TNF-α, and this breakdown was suppressed by SB203580 in polarized RPEs. These results indicate that the breakdown of the RPE barrier function was caused by TNF-α exclusively in polarized RPEs, and TNF-α was acting through the p38 MAPK pathways. Investigations of polarized should be more suitable for studying the pathophysiology of RPE cells in vitro.