P18 Induction of matrix metalloproteinases in non-pigmented ciliary epithelium by tumor necrosis factor-alpha was counteracted by infliximab

Masahiro Zako 1, Hiroshi Yamada 1, Shingo Inaguma 2, Masayoshi Iwaki 1, Masahiko Yoneda 3

Department of Ophthalmology, Aichi Medical University

Infliximab, a monoclonal antibody directed against human tumor necrosis factor-alpha (TNF-α), effectively treats anterior uveitis, which can accompany Behcet's disease. Here, we investigated the underlying mechanism of this action. We examined human non-pigmented ciliary epithelial cells (HNPCECs), which make up the blood-aqueous barrier (BAB) in the uvea. We measured the expression levels of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs in the presence or absence of TNF-α using quantitative real-time polymerase chain reaction and enzyme-linked immunosorbent assays. The expression of MMP-1, MMP-3, and MMP-9 increased in the presence of TNF-α and the addition of infliximab reversed the increase. The TNF-α effects were more attenuated when infliximab was added before than when it was added after TNF-α exposure. Gelatin zymography demonstrated that the protease activity of these MMPs was also increased in the presence of TNF-α and attenuated with infliximab. Immunostaining showed that MMP-1, MMP-3, and MMP-9 degraded claudin-1 and occludin in HNPCECs and in non-pigmented ciliary epithelial cells of the swine ciliary body. In a monolayer of HNPCECs, we found that permeability was significantly increased with MMP treatment. Thus, TNF-α increased levels of MMPs in cells that form the BAB, and MMPs degraded components of the tight junctions in the BAB, which increased permeability through the cellular barrier. Furthermore, infliximab effectively attenuated the TNF-α-induced increases in MMP expression in cells that make up the BAB. These findings might suggest a basis for the clinical prevention of anterior uveitis.