THE ROLE OF ERK-MAPK PATHWAY IN TH17 DIFFERENTIATION AND THE PATHOGENESIS OF COLITIS

Hou-Pu Liu¹, Yingzi Cong¹,²

Departments of Microbiology and Immunology¹, Pathology², University of Texas Medical Branch, Galveston, TX

Driven by antigen stimulation and cytokine milieu, naïve T cells differentiate into different subsets of effector T cells. Recently Th17 cells have been implicated in many autoimmune diseases as well as inflammatory bowel diseases (IBD). Two Th17 skewing conditions are defined. The combination of TGF-β and IL-6, and the combination of IL-1β, IL-23 plus IL-6 can induce Th17 generation. Although the MAPK pathway is involved in the signaling of TGF-β, IL-6 and IL-1β, it is still unknown whether it regulates differentiation of Th17 cells. Besides, blockade of TGF-β signaling inhibits Th17 differentiation while blockade of Smad4, a dominant downstream molecule, has no influence, which indicates the possible key roles of Smad-independent pathways in Th17 development. ERK-MAPK is one of the major Smad-independent pathways. In this study, we investigated the impacts of ERK-MAPK on Th17 differentiation. In CD4 T cell cultures, we blocked the activation of ERK by administrating ERK selective inhibitor or by utilizing siRNA knockdown and assessed the changes on functions and phenotypes in Th17 cells by flow cytometry, ELISA and real-time-PCR. We found the blockade of ERK activation inhibited Th17 cell differentiation in both Th17 polarizing conditions. In TGF-β plus IL-6 condition, the inhibition on IL-6 mediated ERK pathway up-regulated FoxP3 expression, which inhibits transcriptional function of Rorγt and thus caused decrease in IL-17A expression. In IL-1β+IL-23+IL-6 condition, the inhibition on IL-6- and IL-1β-mediated ERK activation down-regulated Rorγt expression. Further, when administrating ERK inhibitor in context of a mouse colitis model, we found decreased numbers of effector CD4 T cells in treated mice than control mice, indicating a lower level of inflammation. In conclusion, these findings indicate that the ERK-MAPK pathway regulates Th17 cells as it promotes Th17 differentiation and the inhibition of ERK-MAPK could provide a new avenue for treatment of autoimmune diseases and IBD.