Clinical significance of CD161+CD4+ T cells in the development of chronic antibody-mediated rejection in kidney transplant recipients

Kyoung-Woon Kim¹, Bo-Mi Kim¹, Kyoung Chan Doh¹, Chan-Duck Kim², Kyung Hwan Jeong³, Sang-Ho Lee³, Chul Woo Yang⁴, Byung Ha Chung⁴

¹Department of Biochemistry & Molecular Biology, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of
²Department of Internal Medicine, Kyungpook National University Hospital, Korea, Republic of
³Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Korea, Republic of
⁴Department of Internal Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of

Objectives: In this study, we investigated whether CD161+CD4+ T cells can reflect the Th17 pathway in kidney transplant recipients (KTRs) and investigated the clinical significance of this cell type in chronic antibody-mediated rejection (cAMR) in KT.

Methods: First, we investigated the relationship between CD161+CD4+ T and Th17 cells by flow cytometry and microarray analysis in an in vitro study. Second, we compared the proportion of T cell subsets including CD161+CD4+ T cells in cAMR (n=18), long-term graft survival (LTGS) (n=46), and interstitial fibrosis/tubular atrophy (IF/TA) (n=22). We compared CD161+ cell infiltration between cAMR and IF/TA and also examined the effect of CD161+ T cells on human renal proximal tubular epithelial cells (HRPTEpiC).

Results: In flow cytometry, the proportion of CD161+CD4+ T cells showed a significant correlation with the proportion of Th17 cells. In microarray analysis, transcripts associated with the Th17 pathway such as IL18RAP, IL-18R1, IL23R, IL12RB2, RORC, TBX21, and EOMES were upregulated in CD161+ cells compared with CD161- cells. In an ex vivo study, only CD161+CD4+ T cells showed a significant increase in the cAMR group compared with IF/TA and LTGS groups. In allograft tissue, CD161+ cells showed a higher level of infiltration in the cAMR group than the IF/TA group. Lastly, CD161+ T cells increased the production of inflammatory cytokines from HRPTEpiC in a dose-dependent manner.

Conclusions: This study suggests that CD161+ T cells can be used as a marker for activation of the Th17 pathway and may play a significant role in the development of cAMR.