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신장이식 환자에서 CD8 조절 T 림프구의 증가를 매개한 mTOR 억제제의 CD4+ Th17 세포경로 억제

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mTOR Inhibitor Suppress CD4+ Th17 Cells by Upregulation of CD8+ Regulatory T Cells in Kidney Transplant Recipients

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Background: Accumulating evidence suggests that Treg/Th17 axis have important role in long term allograft survival in kidney transplantation. The aim of this study is to compare the effect between tacrolimus (Tac) and sirolimus (SRL) in the regulation of Treg/Th17 axis.

Methods: First, Th17 (CD4+IL-17+ T) and Treg (CD4+Foxp3+ T) cells were quantitatively determined upon T-cell-specific stimulation in blood mononuclear cells (PBMCs) from healthy individuals (n=21; in vitro) and kidney-transplant patients (n=14; in vitro, ex vivo) under clinically relevant concentrations of SRL or Tac. Second, we investigated the change of T cell subset after conversion from Tac to SRL in vivo. Third, in search for CD8 subpopulations with regulatory functions (CD8+CCR7+CD8+ T (CD8+Treg)) induced by SRL, we investigated its suppressive effect on allogeneic CD4+ T cells.

Results: In vitro, SRL suppressed Th17 cells in a concentration-dependent manner, but did not suppress Treg cells even at high concentration. Tac suppressed Treg cells in a concentration-dependent manner, but did not suppress Th17 cells even at high concentration. In vivo study, the proportion of Th17 cells and CD8+Treg showed significant increase, but Th2 cells and effector memory CD8+T cells showed significant decrease after conversion from Tac to SRL. In vitro study in search for the CD8+ Treg cells, SRL was able to expand CD8 subphenotypes. In addition, induced CD8+Treg cells significantly inhibited allogeneic CD4+T cells and also down-regulated the IL-17 production from CD4+ T cells.

Conclusion: This study suggests that SRL, mTOR inhibitor suppress CD4+ Th17 cells by upregulation of CD8+ Regulatory T cells in kidney transplant recipients.

Key Words: mTOR 억제제, Th17 세포, 조절 CD8+ T 세포
mTOR inhibitor, Th17 cell, CD8+ regulatory T cell