KSN 2016 Abstract Submission

Transplantation & Immunology

KSN2016ABS-1445

Vitamin D suppresses effector T cell induced inflammation in human renal proximal tubular epithelial cells

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Background: The aim of this study was to investigate the effects of Vitamin D pretreatment on inflammatory response in human proximal renal tubular epithelial cells (HRPTEpiCs) induced by effector T cells or inflammatory cytokines.

Methods: First, we investigated the effect of 1α,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3] on CD4+ T cell proliferation by FACs analysis and ELISA. Second, we investigated the effect of 1,25$(OH)_2$D3 on IL-6, IL-8, KIM-1 and Fibronectin 1 expression in HRPTEpiCs, co-coultured with/without activated CD4+T cells using ELISA and real-time PCR and we analyzed mTOR/STAT3 signaling as a potential mechanism by which 1,25$(OH)_2$D3 exerts its effect on HRPTEpiCs. Lastly, we divided 90 kidney transplant recipients (KTR) into low or normal group according to serum 25-hydroxyvitamin D (25(OH)D) level (<20 ng/mL or not) and compared urine inflammatory-cytokine (IL-6, IL-8) or KIM-1 level between 2 groups.

Results: Pre-incubation with 1,25$(OH)_2$D3 significantly reduced the percentage of Th1 and Th17 cells compared to Th0 condition ($P<0.05$ for each). In contrast, 1,25$(OH)_2$D3 increased the proportion of Th2 and Treg cells in a dose dependent manner ($P<0.05$ for each). To evaluate the direct protective effect of vitamin D on the target organ, we investigated whether vitamin D protects HRPTEpiCs against inflammatory cytokine or effector T cell-induced inflammation. Our results showed that inflammatory cytokines (TNF-a, IL-17 and TGF-b) induced IL-6, IL-8 or KIM-1 production from HRPTEpiCs in a dose-dependent manner. Treatment with 1,25$(OH)_2$D3 significantly reduced the level of these cytokines ($P<0.05$ for all). In western blot analysis, mTOR/STAT3 pathway was down-regulated by 1,25$(OH)_2$D3 in HRPTEpiCs. Lastly, the concentration of urine IL-6/creatinine ($p < 0.05$) and Kim-1/creatinine ($p < 0.05$) was higher in low 25(OH)D group (n=41)) than in normal 25(OH)D group (n=49) in KTRs.

Conclusion: In conclusion, we suggest that treatment with 1α,25-dihydroxyvitamin D3 (1,25$(OH)_2$D3) could be a new therapeutic strategy to reduce allograft tubule cell injury by effector T cells in kidney transplantation.

Keywords: Effector T cells, human renal proximal tubular epithalial cells, Vitamin D