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Mycophenolate Mofetil Attenuates Diabetic Kidney Injury by Depression of Renal T Lymphocyte

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Background: Mycophenolate mofetil (MMF) is a reversible inhibitor of inosine monophosphate dehydrogenase in purine biosynthesis which is necessary for the of T cells proliferation. Recent studies reported that proinflammatory T helper 1 (Th1) and T helper 17 (Th17) cell subsets have been associated with the pathogenesis of metabolic disease. However, the role of Th1 and Th17 cells in the development and progression of diabetic nephroapathy remains unknown. In this study, we investigated the hypothesis that MMF attenuates diabetic kidney injury by modulation of renal T cell proliferation and related cytokine.

Methods: We designed four animal groups as following; 1) C57BL/6 (Control); 2) Control+MMF (30 mg/kg/day); 3) Streptozotocin-induced diabetic mice (STZ); 4) STZ+MMF for 12 weeks. IFN-ɣ and IL-17 producing kidney mononuclear cell was assessed by flow cytometry. Using immunohistochemistry staining, CD4+, CD8+ T cell, and CD20+ cells infiltration in kidney was measured. Cell proliferation was assessed by BrdU stating. IFN-ɣ, IL-4, IL-17, IL-1β, IL-6, IL-10 and TNF-α were investigated in kidney tissue and serum by Mouse Cytokine Magnetic Bead Panel.

Results: Urinary albumin excretion and mesangial expansion decreased in STZ+MMF compared to STZ without change of HbA1c level. In immunohistochemistry, increased numbers of kidney interstitial CD4+, CD8+ T cells and CD20+ cells were identified in diabetic mice. BrdU incorporation was detected by subsequent intracellular staining of single cell suspensions from kidney, and consequently, CD4+ T cell proliferation was reduced in STZ+MMF. In flow cytometry of kidney mononuclear cell, diabetic mice showed an increase of IFN-ɣ for Th1 cells and IL-17 for Th17 cells at 16 weeks. The production of IL-17 was reduced by MMF while no significant difference was observed in IFN-ɣ production. The seven cytokines (IFN-ɣ, IL-4, IL-17, IL-1β, IL-6, IL-10 and TNF-α), analyzed by multiplex assay, in serum and kidney tissue samples were significantly increased in diabetic mice. These CD4+ related cytokines were reduced in serum by systemic effect of MMF, whereas only IL-17 production was inhibited in kidney by MMF.

Conclusion: Our study results indicated that MMF attenuates renal inflammation by depression of renal IL-17 production in diabetic mice.

Key Words: 당뇨병성 신증, MMF, IL-17
Diabetic nephropathy, Mycophenolate mofetil (MMF), IL-17