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신허혈재관류 손상에서 FTY720 투여시 조절T임파구를 통한 관용유도

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CD4+ CD25+ Regulatory T Cell Might Partially Mediate Beneficial Effect of FTY720 in Ischemia/reperfusion Induced Acute Kidney Injury

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Inflammation contributes to pathogenesis of kidney I/R injury. Synthetic sphingosine analog of myriocin, FTY 720 has recently been introduced and known to attenuate I/R injury via inducing peripheral T cell depletion. However, several recent studies suggest that anti-inflammatory effect of FTY 720 might be associated with tolerogenic activity by modulating dendritic cell function or direct effect on CD4+ CD25+ Tregs. Therefore, the purpose of this study was to examine the role of dendritic cell or Tregs in FTY 720 induced beneficial effect in I/R induced AKI. C57/BL6 mice underwent bilateral ischemia (30 min) and FTY 720 or vehicle was administered before I/R injury. Twenty four hours after reperfusion, biochemical, histological kidney damage was assessed along with tissue cytokines and chemokines by cytometric bead array. Percent Tregs or Foxp3 mRNA expression was examined in kidney and spleen by flow cytometry or real time QPCR. Percent CD11b+ CD11c+ dendritic cells or dendritic cell phenotypes in blood/spleen was examined and compared between vehicle or FTY720 treated animals. As expected, treatment with FTY 720 attenuated I/R induced kidney injury and also kidney CD4 T cell infiltration with simulataneous decrease in tissue proinflammatory cytokines. In addition to peripheral T cell depletion, FTY 720 treated animals showed higher frequency of CD4+ CD25+ Tregs with prominent upregulation of Foxp3 mRNA expression in spleen. Furthermore, FTY720 treatment resulted in significant increase in peripheral blood tolerogenic CD11b+ CD11c+ myeloid DC and also induced spleen derived CD11c+ DC activation determined by CD80 or CD86 expression. These results suggest that beneficial effect of FTY 720 in I/R injury might be partially mediated by dendritic cell modulation or increasing Treg activity and further studies identifying tolerance induction mechanisms might be useful in developing various strategies in prevention or treatment of AKI.

Key Words : FTY720, 조절T임파구, 수지상세포
FTY720, Regulatory T cell, Dendritic cell