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Sulfatide에 의해 활성화된 Type II NKT세포가 허혈 및 재관류 후 신기능에 미치는 영향

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Sulfatide-reative Type II NKT Cells Regulate Renal Ischemia Reperfusion Injury

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Background and Methods : Natural killer T (NKT) cells expressing semi- invariant CD1d- reactive TCR have been known to exert protective roles in the autoimmune and infectious diseases. NKT cells produce multiple cytokines and confer protection in immune- mediated disorders upon activation. Although α - Galactosylceramide (α - GalCer) derived from the marine sponge has been known to stimulate type I NKT cells, little is known for the way and role of activation in type II NKT cells. Here, we have evaluated the regulatory specificity of sulfatide- reactive type II NKT cells using a mouse renal ischemia reperfusion injury (IRI) model. IRI was induced in C57BL/6 (B6), NKT cell deficient mice (B6.CD1dP$^{-/-}$) and type I NKT cells deficient mice (B6.Jα 281$^{-/-}$) by utilizing bilateral renal pedicle clamping (30 min) or sham ischemia.

Results : B6.CD1d$^{-/-}$ mice showed a distinctively accelerated acute kidney injury (AKI) compared to wild type mice (serum BUN 168.8±5.97 mg/dL vs. 101.4±10.57, $p<0.05$) by the induction of disease. But the repletion of NKT cells into B6.CD1d$^{-/-}$ mice by adoptive transfer of hepatic NKT cells, lessened the severity of AKI similar to wild type mice (serum BUN 101.4±10.57 mg/dL vs. 88.43±6.2, p=ns). With the utilization of glycolipid/CD1d dimer and cytokine responses, the activation of sulfatide- reative type II NKT cells on B6.Jα 281$^{-/-}$ mice was also effective to protect renal function and prevent from inflammatory responses compared to non- treated deficient mice. Kidneys from B6.Jα 281$^{-/-}$ mice where activated sulfatide- reative type II NKT cells were adoptively transferred had less tubular epithelial necrosis, tubulointerstitial fibrosis, and macrophage infiltration than non-treated deficient mice in a dose- dependent manner. Fluorescent- labeled NKT cells were distributed in tubulointerstitial area which was damaged by IRI. The adoptive transfer of NKT cells or treatment of sulfatide into injured B6. Jα 281$^{-/-}$ mice was significantly reduced activation of T cells on kidney. Hepatic NKT cells secreting abundant IL- 4, IL- 10 and IL- 13 with the activation by sulfatide, suppressed the proliferation of lymphocytes driven by CD3 stimulation. The adoptive transfer of sulfatide- reative type II NKT cells into B6.CD1d$^{-/-}$ mice attenuated the severity of IRI along with the reduced expression of TGF- β 1 and IFN- γ in kidney.

Conclusion : These findings highlight the CD1d- dependent NKT cells have the direct regulatory capacity in experimental AKI, thus suggesting a feasible cellular targets to protect kidneys from ischemic injury.

Key Words : 허혈 및 재관류, NKT세포, 면역조절
Sulfatide, type II NKT, IRI