F-B1

허혈/재관류 콩팥 손상에서 sulfatide 반응성 NKT 세포의 방어적 역할

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The Protective Roles of Sulfatide-reactive NKT Cells on Ischemia/reperfusion Injury in Kidney

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Background and Methods : Natural killer T (NKT) cells expressing semi-invariant TCR have been reported to exert various effects on the autoimmune and infectious diseases, but little is known for the specific role according to the subtype of NKT cells. We tried to evaluate the role of subtype of NKT cells on a renal ischemia reperfusion injury (IRI) model. The subtype of NKT cells was utilized either by C57BL/6 (B6), type I/II NKT cells deficient mice (B6.CD1d-/-) or type I NKT cells deficient mice (B6.Jα281-/-). IRI was induced by bilateral renal pedicle clamping.

Results : B6.CD1d-/- mice showed more severe ischemic renal injury compared to wild type mice (BUN 169$\pm$6.02 mg/dL vs. 105$\pm$9.83, $p<0.05$). However, the adoptive transfer of hepatic NKT cells into B6.CD1d-/- mice lessened the injury similar to the level of wild type mice (BUN 105$\pm$9.83 mg/dL vs. 90$\pm$5.4, p=ns). The activation of type II NKT cells by sulfatide which is the specific activator, on B6.Jα281-/- mice was confirmed by glycolipid/CD1d dimer and cytokine responses. The adoptive transfer of sulfatide-activated type II NKT cells made B6.Jα281-/- mice to have less tubular epithelial disruption, tubular cell apoptosis, macrophage infiltration, and caspase-3 activation in the kidney after IRI. Fluorescent-labeled NKT cells were distributed in the tubulointerstitial area, the main site for ischemic injury. The adoptive transfer of NKT cells or sulfatide treatment significantly reduced the activation of T cells and the expression of TGF-β, IFN-γ and MCP-1 in the injured B6.Jα281-/- kidney. Cultured hepatic NKT cells secreted abundant IL-4, IL-10 and IL-13 by activation with sulfatide, and the activated NKT cells suppressed the anti-CD3-driven lymphocyte proliferation. In transient hypoxia, sulfatide-reactive type II NKT cells from mice and humans attenuated the apoptosis of tubular cells. Also, the expression of proinflammatory cytokines was ameliorated in a hypoxia-inducible factor (HIF)-1α-dependent fashion.

Conclusion : These findings highlight that sulfatide-reactive type II NKT cells participate in an acute ischemic kidney injury in a HIF related manner, thus suggesting a feasible cellular target to protect kidneys from hypoxic injury.

Key Words : 허혈/재관류 손상, 셀파타이드, NKT세포
Ischemia/reperfusion injury, Sulfatide, NKT cell