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Regulatory T Cells Recruited to the Kidney by N,N-dimethylsphingosine Ameliorate Lipopolysaccharide-induced Acute Kidney Injury

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Objective: Regulatory T cells (Tregs) play a role in immunologic tolerance and have the potential to prevent inflammatory diseases by suppress immune responses. The purpose of this study was to examine the effect of N,N-dimethylsphingosine (DMS), a sphingosine kinase inhibitor, on lipopolysaccharide (LPS)-induced kidney inflammation and to explore the underlying molecular mechanisms.

Materials & Methods: Mice were treated LPS (100 mg/kg, intraperitoneally) with or without pretreatment with DMS (0.4 mg/kg, intraperitoneally). The expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and endothelin-1 (ED-1) was determined by immunoblotting and immunohistochemical staining. The mRNA level of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interferon-ɣ (IFN-ɣ), and Foxp3 was measured by real-time PCR. Using flow cytometry analysis, we investigated the expression of CD4+ CD25+ Tregs in mice spleen.

Results: Plasma creatinine level was increased after LPS injection for 12 h compared with controls, which was attenuated in pretreatment with DMS. LPS upregulated CD4+ CD25+ Treg in the spleen, but downregulated Foxp3 mRNA level in the kidney. DMS induced both CD4+ CD25+ Tregs in the spleen and the level of Foxp3 in the kidney. The expression of COX-2, iNOS, and ED-1 in mice kidneys was increased in LPS group, which was downregulated by DMS pretreatment. LPS-induced increased mRNA expression of IL-1β, IL-6, MCP-1 and IFN-ɣ mRNA was attenuated by DMS pretreatment.

Conclusions: DMS ameliorates inflammation in LPS-induced kidney injury by decreasing inflammatory cytokines production, modulating infiltration of Tregs from spleen to kidney. Thus, DMS may protect against the acute kidney injury caused by LPS.

Key Words: Acute kidney injury, DMS, LPS