2-YIA-44 YIA

Prostaglandin $F_{2\alpha}$ receptor antagonist attenuated LPS-induced sepsis in mice.

Toko Maehara, Fumiyoshi Higashitarumi, Risa Kondo, Ko Fujimori

Dept. Pathobiochem., Osaka Univ. Pharmaceut. Sci.

Sepsis is systemic inflammatory response syndrome caused by invasive infection. Although it is known that prostaglandin (PG)$F_{2\alpha}$ level is elevated in the plasma of the patients with sepsis, its role in the sepsis remains unclear. We aimed to investigate the role of $PGF_{2\alpha}$ receptor (FP) signaling in lipopolysaccharide (LPS)-induced sepsis using FP receptor antagonist AL8810 in mice. Sepsis was induced by intraperitoneal injection of LPS (5 mg/kg). AL8810 (10 mg/kg) was intraperitoneally administered at 30 min before LPS injection. Mice were monitored to detect the response to LPS for 24 hours. LPS administration promoted $PGF_{2\alpha}$ production in peritoneal lavage fluid (PLF). At 6 hours after LPS administration, the number of macrophages and neutrophils in PLF was increased, as compared with naïve mice. AL8810 administration enhanced neutrophil migration, but not macrophage migration, in PLF. At 24 hours after injection, there was no difference in number of these cells between LPS and/or AL8810-administered mice. At 24 hours after LPS administration, the mRNA expression of proinflammatory cytokines such as IL-6, TNF-α, IL-1β, and CXCL2 in lung and liver was elevated. Conversely, they were decreased in AL8810-administered mice. It is known that IL-10 decreased excessive inflammatory responses in the acute phase of sepsis. At 3-6 hours after LPS administration, IL-10 levels in PLF were increased, as compared with naïve mice. AL8810 administration enhanced IL-10 production further. In addition, immunostaining showed that Gr-1-positive neutrophils in PLF expressed IL-10. Then, anti-IL-10 antibody administration increased LPS-induced IL-6 and CXCL-2 expression as well as AL8810-decreased these gene expressions. The findings suggest that FP receptor antagonist attenuated LPS-induced sepsis by increasing neutrophil-derived anti-inflammatory cytokine IL-10 production.