Disrupting ceramide-LMIR3 interaction prevents bacterial sepsis by stimulating neutrophil recruitment

An inhibitory receptor LMIR3/CD300f is mainly expressed in myeloid cells, including mast cells and neutrophils. We have recently demonstrated that ceramide-LMIR3 binding inhibits IgE- and mast cell-dependent allergic responses. Sepsis remains a major clinical problem. Negative regulation of innate immunity is associated with sepsis progression. Here we identify the critical role of ceramide-LMIR3 binding in suppressing innate host responses. LMIR3−/− mice were protected against lethality after cecal ligation and puncture (CLP), a murine model of septic peritonitis. In the peritoneal cavity of CLP-operated LMIR3−/− mice, mast cells and recruited neutrophils released high levels of neutrophil chemoattractants, leading to enhanced recruitment of neutrophils that efficiently eliminated Escherichia coli. Ceramide-LMIR3 interaction suppressed such release from Escherichia coli-stimulated mast cells and neutrophils. Importantly, treatment with ceramide antibody or LMIR3-Fc, which disrupted the ceramide-LMIR3 interaction, prevented CLP-induced sepsis by profoundly stimulating neutrophil recruitment. Thus, LMIR3 is an attractive target for the treatment of sepsis.