CC chemokine receptor 2 regulates leukocyte recruitment and IL-10 production during acute polymicrobial sepsis.

Abstract:
Chemokine receptors are important for recruiting leukocytes to sites of infection and may contribute to immune cell activation. The present study investigated the role of the chemokine receptor CCR2 in polymicrobial septic peritonitis. The results showed that peritoneal production of the CCR2 ligands CCL2 and CCL12 in septic mice was largely independent of the common Toll-like receptor signaling adaptor MyD88. Antibody blockade of CCR2 reduced the recruitment of macrophages and neutrophils to the infected peritoneal cavities of both wild-type and MyD88-deficient mice, suggesting that CCR2 engagement contributes to the MyD88-independent cellular response against polymicrobial septic peritonitis. Notably, administration of blocking CCR2 antibodies markedly increased local and systemic IL-10 levels in septic wild-type mice, whereas IL-10 was not detected in MyD88-deficient mice irrespective of whether CCR2 was blocked or not. Inhibition of CCR2 directly augmented Toll-like receptor-induced IL-10, but not TNF and IL-6, production of macrophages in vitro. Concomitant with enhanced IL-10 production, CCR2 blockade caused impaired bacterial clearance and aggravated kidney injury in wild-type, but not MyD88-null mice. These results indicate that CCR2 engagement modulates the innate immune response to polymicrobial septic peritonitis by both...
MyD88-dependent and -independent processes and suggest that a major function of CCR2 in sepsis is to attenuate IL-10 production and IL-10-mediated suppression of host defense.