Detrimental role of CC chemokine receptor 4 in murine polymicrobial sepsis.

Abstract:
CC chemokine receptor 4 (CCR4) and its two ligands, CCL17 and CCL22, are critically involved in different immune processes. In models of lipopolysaccharide-induced shock, CCR4-deficient (CCR4(-/-)) mice showed improved survival rates associated with attenuated proinflammatory cytokine release. Using CCR4(-/-) mice with a C57BL/6 background, this study describes for the first time the role of CCR4 in a murine model of polymicrobial abdominal sepsis, the colon ascendens stent peritonitis (CASP). CASP-induced sepsis led to a massive downregulation of CCR4 in lymphoid and nonlymphoid tissues, whereas the expression of CCL17 and CCL22 was independent of the presence of CCR4. After CASP, CCR4(-/-) animals showed a strongly enhanced bacterial clearance in several organs but not in the peritoneal lavage fluid and the blood. In addition, significantly reduced levels of proinflammatory cytokines/chemokines were measured in organ supernatants as well as in the sera of CCR4(-/-) mice. CCR4 deficiency consequently resulted in an attenuated severity of systemic sepsis and a strongly improved survival rate after CASP or CASP with intervention. Thus, our data provide clear evidence that CCR4 plays a strictly detrimental role in the course of polymicrobial sepsis.