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Pathogen recognition and triggering of the inflammatory response following infection in mammals depend mainly on Toll-like and Nod-like receptors. Here, we evaluated the role of Nod1, Nod2 and MyD88-dependent signaling in the chemokine production and neutrophil recruitment to the infectious site during sepsis induced by cecal ligation and puncture (CLP) in C57Bl/6 mice. We demonstrate that Nod1 and Nod2 are not involved in the release of chemokines and recruitment of neutrophils to the infectious site during CLP-induced septic peritonitis because these events were similar in wild-type, Nod1-, Nod2-, Nod1/Nod2- and Rip2-deficient mice. Consequently, the local and systemic bacterial loads were not altered. Accordingly, neither Nod1 nor Nod2 was involved in the production of the circulating cytokines and in the accumulation of leukocytes in the lungs. By contrast, we showed that MyD88-dependent signaling is crucial for the establishment of the local inflammatory response during CLP-induced sepsis. MyD88-deficient mice were susceptible to sepsis because of an impaired local production of chemokines and defective neutrophil recruitment to the infection site. Altogether, these data show that Nod1, Nod2 and Rip2 are not required for local chemokine production and neutrophil recruitment during CLP-induced sepsis, and they reinforce the importance of MyD88-dependent signaling for initiation of a protective host response.