
**Abstract**

The importance of peptidoglycan detection in the host innate immune response has long been underestimated. However, the recent identification of proteins involved in the sensing of peptidoglycan in both mammals and *Drosophila* has revealed that the detection of this microbial motif is key to the defense response. In *Drosophila*, the peptidoglycan-recognition proteins (PGRP) are the initial sensors of infecting bacteria that then trigger a cascade ultimately leading to the expression of antimicrobial peptides. In mammals, PGRP also exist and although they bind peptidoglycan, the role of these proteins in innate immune responses remains to be clearly defined. In contrast, the Nod proteins (Nod1 and Nod2), which are also involved in peptidoglycan sensing, appear to play a key role in innate immunity against bacteria by triggering host defense responses through the activation of the transcription factor, NF-κB. Interestingly, mutations in Nod2 are related to increased susceptibility to Crohn’s disease, thereby implicating defective bacterial sensing in the development of this chronic disease. In this review, we will focus on the recent findings concerning mammalian and *Drosophila* proteins involved in peptidoglycan recognition and the putative role of these proteins in the innate immune defense response.