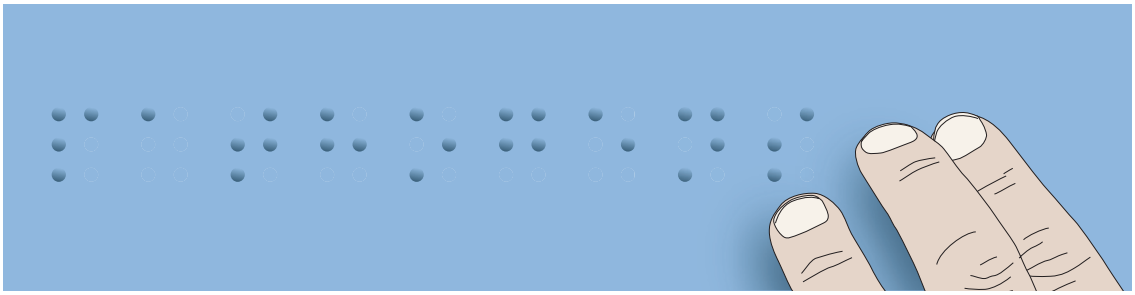
Nature Reviews Immunology | AOP, published online 9 September 2011; doi:10.1038/nri3069



INFLAMMASOME

NAIPs: pathogen-sensing proteins

Since they were first described less than 10 years ago, inflammasomes have become central to the working model of how the innate immune system senses and responds to pathogens and tissue injury. However, it remains unclear how individual inflammasomes are activated by specific stimuli. Writing in *Nature*, Kofoed and Vance suggest that NAIP (NLR family, apoptosis inhibitory protein) family members function as pathogen sensors that dictate the activation of the NLRC4 (NLR family, CARD-containing 4) inflammasome.

The NLRC4 inflammasome mediates caspase 1-dependent inflammatory cytokine production and pyroptosis (a form of cell death) in response to bacterial flagellin and the inner rod of the type III secretion systems of various bacterial species. However, a lack of evidence showing that NLRC4 directly recognizes these bacterial products raises the possibility that other molecules might be involved.

The authors focused on the NAIP family of proteins, as NAIP5 has been shown to be involved in the NLRC4-mediated response to flagellin but not to PrgJ (the rod component of a type III secretion system of *Salmonella enterica* serovar Typhimurium). Using a short hairpin RNA-mediated knockdown approach, they found that *Naip2* is specifically required for PrgJ-mediated NLRC4 inflammasome activation in macrophages, whereas *Naip5* is required for the response to flagellin.

The authors next reconstituted non-immune 293T cells with NAIP5, NLRC4, caspase 1 and/or flagellin from *Legionella pneumophila* to eliminate any redundancy between NAIP family members that might exist in macrophages. NAIP5 was shown to promote NLRC4 oligomerization in response to flagellin, resulting in the formation of a multiprotein complex containing NAIP5, NLRC4 and flagellin. By contrast, PrgJ did not induce oligomerization of NAIP5–NLRC4, but when the cells were reconstituted with NAIP2 instead of NAIP5, oligomerization occurred. Furthermore, NAIP6 could substitute for NAIP5 in mediating the response to flagellin. So, NAIP5 and NAIP6 activate NLRC4 in response to flagellin, whereas NAIP2 is required for inflammasome activation by PrgJ.

Together, these data lead the authors to suggest a model in which NAIP proteins function as direct receptors for bacterial ligands and in which the main function of NLRC4 is to serve as an adaptor molecule downstream of the ligand–receptor interaction. This study has important implications for our understanding of pathogen recognition and inflammasome activation.

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ORIGINAL RESEARCH PAPER Kofoed, E. M. & Vance, R. E. Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity. *Nature* 28 Aug 2011 (doi:10.1038/nature10394)