INNATE IMMUNITY

New PAMP discovered

Host defence against invading pathogens is initiated by the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), which drives pro-inflammatory innate immune responses to eliminate the pathogen and instruct the adaptive immune system. Reporting in *Science*, Gray-Owen and colleagues show that a Gram-negative bacteria-derived monosaccharide — D-glycero-β-D-manno-heptose-1,7-bisphosphate (HBP) — is a PAMP that drives nuclear factor-κB (NF-κB)-mediated inflammatory responses through activation of the signalling molecule TIFA (TRAF-interacting protein with FHA domain-containing protein A).

> HBP ... promotes inflammation independently of the main PRR pathways

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Previous studies have suggested that a metabolite generated in the ADP–heptose biosynthetic pathway and shed by *Neisseria* spp. can activate the NF-κB pathway in mammalian cell lines. Here, the authors identified HBP as the pro-inflammatory metabolite. The kinetics of HBP-induced NF-κB activation were slower than those induced by extracellular PAMPs, suggesting that HBP first requires entry into the cytosol. Indeed, HBP was shown to enter cells via dynamin-dependent endocytosis to trigger NF-κB activation and induce pro-inflammatory cytokine production.

HBP is conserved across numerous bacterial species but is absent from eukaryotic cells. However, unlike *Neisseria* spp., other Gram-negative bacteria do not release HBP. Cell lysates of several bacterial species, including *Escherichia coli*, were shown to activate NF-κB in 293T cells, and this effect was dependent on HBP. Further analysis showed that internalization and degradation of *E. coli* in THP1 monocytic cells deficient for the main PRR adaptor proteins MYD88 and TRIF resulted in the HBP-mediated enhancement of interleukin-6 (IL-6) production. This suggests that HBP is released during bacterial lysis in phagolysosomes and promotes inflammation independently of the main PRR pathways.

So, how does HBP promote NF-κB activation? A series of biochemical analyses showed that treatment of cells with HBP results in the phosphorylation of TIFA at an evolutionarily conserved amino acid (Thr9), which triggers TIFA oligomerization at lysosomal compartments. This promotes the binding of the adaptor molecule TNFR-associated factor 6 (TRAF6), induction of its E3 ubiquitin ligase activity and stimulation of the canonical NF-κB pathway via activation of the kinases TAK1, IκBβ and IκBγ. Whether TIFA directly senses HBP or whether it is a proximal adaptor in the signalling cascade remains to be determined.

Finally, the authors investigated the *in vivo* relevance of HBP sensing. Injection of HBP-containing supernatant devoid of other PAMPs into the dorsal air pouch of mice induced pro-inflammatory cytokine production and neutrophil recruitment. Furthermore, challenge of mice with a strain of *N. meningitidis* lacking HBP induced significantly less meningococcal IgG following rechallenge than a HBP-sufficient strain.

Together, these data show that HBP is a PAMP, the detection of which in the cytosol promotes TIFA-dependent immunity to Gram-negative bacteria.

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ORIGINAL RESEARCH PAPER Gaudet, R. G. *et al.* Cytosolic detection of the bacterial metabolite HBP activates TIFA-dependent innate immunity. *Science* **348**, 1251–1255 (2015)