To investigate how planetary magnetic fields are generated, it is now possible to solve the fundamental equations that govern the fluid flows and the magnetic fields inside planets. The basic principles of dynamo action were laid down a century ago[11], but solving the fluid–dynamo equations proved difficult. Computers have been able to handle the calculations required to model Earth's dynamo only since 1995 (ref. 12). Nevertheless, much progress has been made, and computational models of dynamos can now capture many of the characteristics of Earth's magnetic field[13].

In the past five years, these models have been adapted to deal with the large variations in density between the interior and atmosphere of Jupiter[6,7], and can now be compared with the field inferred by Moore and colleagues. However, dynamo models depend on the internal structure of the planet, which in turn depends on the planet's thermodynamic properties, electrical-conductivity profile and composition. Although these issues have been extensively explored, some uncertainty remains. Models of fields that are dipolar but broadly symmetric about the equator have been developed[6], as have models of fields that are asymmetric but not dipolar[14]. The challenge is therefore to formulate models of fields that are both asymmetric and dipolar.

Moore and colleagues' suggested explanations for Jupiter's field morphology can now be tested by dynamo modellers to discover whether the explanations are indeed compatible with Juno's observations. Exciting times lie ahead for the study of the interiors of giant planets, as modellers digest the information coming from Juno and begin to work out a clearer picture of the inside of Jupiter. ■

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IMMUNOLOGY

An immune response with a sweet tooth

A previously unknown pathway that enables mammalian cells to recognize infection and trigger an immune response requires a kinase enzyme in the host cell to bind a sugar molecule produced by infecting bacteria. SEE LETTER P.122

JOHN-DEMIAN SAUER

Bacterial infections are a major cause of disease and death worldwide. The innate branch of the mammalian immune system, which recognizes and reacts to general characteristics of pathogenic organisms, has a key protective role. On page 122, Zhou *et al.*[1] describe a mechanism by which the innate immune system is activated in response to bacterial sugar molecules. This finding broadens our understanding of the types of molecule that can be recognized as hallmarks of bacterial infection and the host proteins that can recognize such molecules.

A key advance in our understanding of how the innate immune system functions was the identification of proteins called pattern-recognition receptors (PRRs), which recognize 'non-self' molecules termed pathogen-associated molecular patterns (PAMPs). Beginning with the Toll and Toll-like receptor PRRs[2–4] in the late 1990s, the identification of PRRs and the PAMPs that they recognize has proceeded at a breathtaking pace.

A key function of PRRs is to help drive the expression of secreted proteins called cytokines, which alert the immune system to the presence of infection. The transcription factor NF-κB is a central regulator of cytokine expression. Zhou and colleagues studied human cells grown *in vitro* to try to identify pathways that activate NF-κB in response to infection by the bacterium *Yersinia pseudotuberculosis*. This bacterium has a needle-like, multiprotein structure called a type III secretion system (T3SS), which is required for the direct transfer of bacterial proteins into host cells. T3SSs are evolutionarily conserved in many pathogenic bacteria.

Zhou *et al.* took an unbiased approach and screened a collection of *Y. pseudotuberculosis* genetic mutants to identify bacterial genes that are linked to NF-κB activation in response to infection. This led the authors to focus on the enzyme HldE, which catalyses steps in the biosynthetic pathway that generates lipopolysaccharide (LPS) molecules.

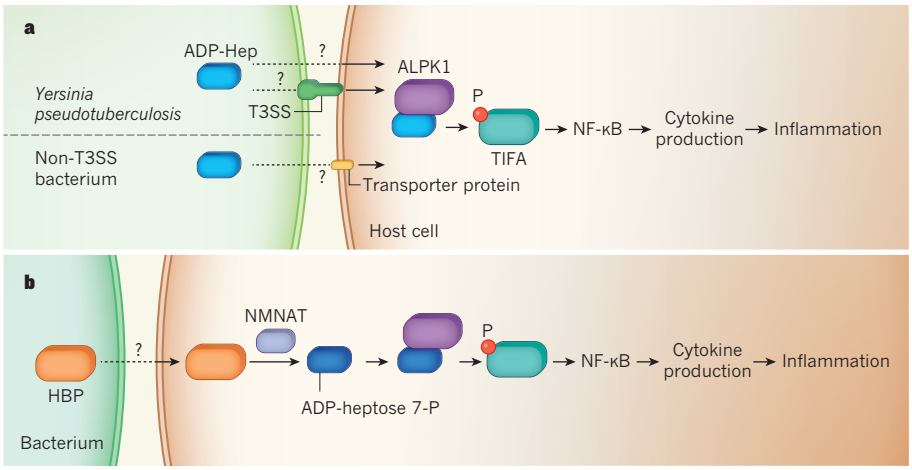

Figure 1 | Bacterial sugars trigger a host immune response. **a**, Zhou *et al.*[1] demonstrate that in bacteria such as *Yersinia pseudotuberculosis*, which has a multiprotein complex called a type III secretion system (T3SS), and in other bacterial species lacking a T3SS, the sugar molecule ADP-β-D-manno-heptose (ADP-Hep) can enter a host cell, by an unknown route (possibly through a transporter protein), and can trigger a signalling pathway that drives inflammation. When ADP-Hep enters the host cell, it binds to ALPK1, which activates the protein TIFA by adding a phosphate group (P) to it. The downstream signalling pathway, not all the steps of which are shown, leads to activation of the protein NF-κB, which drives the expression of cytokine proteins that stimulate an immune response to the infection. **b**, The authors also report that if the bacterially produced sugar D-glycero-β-D-manno-heptose 1,7-bisphosphate (HBP) enters the host cell (by a route that remains to be determined), it can be converted by host enzymes of the NMNAT family into the molecule ADP-heptose 7-P. This binds to ALPK1 and activates the same pathway as that activated by ADP-Hep.

LPS is an essential component of the cell surface of a subset of bacterial pathogens called Gram-negative bacteria.

Using genetically mutated bacteria and purified sugar molecules, the authors sought to pinpoint the molecules in the LPS biosynthetic pathway that stimulate NF-κB activation. They found that the presence of bacterial sugars, including ADP-β-D-manno-heptose (ADP-Hep) and D-glycero-β-D-manno-heptose 1,7-bisphosphate (HBP), in the host-cell cytoplasm triggered NF-κB activation. This is consistent with a study[5] of *Neisseria meningitidis* bacteria that demonstrated that HBP can trigger NF-κB responses in host cells. Crucially, Zhou *et al.* showed that ADP-Hep is 100 times more potent than is HBP at activating NF-κB. They found that addition of ADP-Hep to the extracellular environment of host cells can activate NF-κB, suggesting that dedicated host-cell transporter proteins deliver ADP-Hep to the host's cytoplasm.

No PRR was known to recognize ADP-Hep. To search for one, the authors used a gene-editing approach to conduct a screen in which they generated random mutations in host cells and tested whether the mutations affected ADP-Hep recognition. They uncovered two candidate genes that respectively encode the kinase enzyme ALPK1 and the protein TIFA, and showed that these are required for NF-κB activation in response to ADP-Hep in host cells (Fig. 1). A previous study had revealed[5] that TIFA is required for recognition of HBP from *N. meningitidis*. ALPK1 and TIFA signalling has also been linked to HBP-dependent host activation of NF-κB in response to infection by the bacteria *Shigella flexneri*[6] and *Helicobacter pylori*[7]. Using biochemical approaches, Zhou and colleagues demonstrated that ADP-Hep binds directly to the amino terminus of ALPK1. The authors solved the X-ray crystal structure of ALPK1 in a complex with ADP-Hep, and validated their structural model by testing the effect of mutations in ALPK1 that were predicted to impair its binding to ADP-Hep.

Zhou *et al.* also generated ALPK1-deficient mice. The NF-κB-dependent production of cytokines was significantly reduced in these animals after challenge with either ADP-Hep or the pathogenic bacterium *Burkholderia cenocepacia*, compared with results seen in animals that were not deficient in ALPK1. Moreover, the number of bacteria in the lungs of mice infected with *B. cenocepacia* was higher in ALPK1-deficient animals than in wild-type mice.

Perhaps Zhou and colleagues' most striking finding is that mammalian adenylyltransferase enzymes, specifically those of the NMNAT family, catalyse a reaction that converts HBP into a molecule called ADP-heptose 7-P, which can act as a ligand by binding to ALPK1. Previous work[5] had suggested that HBP is a PAMP that can directly activate NF-κB. Although HBP can be defined as a PAMP, given that it is a bacterially derived molecule that triggers a host response, Zhou and colleagues' data indicate that HBP must be converted to ADP-heptose 7-P by host enzymes to trigger this response. The authors report slight differences in the way in which ADP-Hep and ADP-heptose 7-P bind to ALPK1, and use these differences to demonstrate why ADP-Hep and not HBP or ADP-heptose 7-P is the relevant ligand for ALPK1-mediated NF-κB activation, at least in *Y. pseudotuberculosis* infection.

Zhou and colleagues' findings have important implications. Evidence that ADP-Hep is a PAMP adds to a growing awareness that bacterial metabolites can act as PAMPs. Given that ADP-Hep is needed to synthesize an essential component of the outer membrane of most Gram-negative bacteria, this makes it an ideal PAMP. However, it is not known how this molecule, which is normally found inside the bacterium, reaches the cytoplasm of the host cell. In *Y. pseudotuberculosis*, this process requires the T3SS, although it is unclear whether ADP-Hep is actively transported or accidentally leaks through the T3SS, or whether it enters by the pores that the T3SS generates in the host-cell membrane.

The authors report that bacterial species that lack a T3SS can still trigger the ALPK1 pathway in an ADP-Hep-dependent manner, consistent with the ability of purified ADP-Hep to activate the pathway by an extracellular route. This suggests that a dedicated transport system might exist that allows the host cell to sample its extracellular surroundings for the presence of this PAMP, similar to the way in which certain extracellular PAMPs are transported to the cytoplasm for recognition by host proteins[8].

Why does bacterial ADP-Hep exposure occur if it activates the innate immune system? Perhaps its release is needed to fulfil some as yet unknown function. Pathogens often evolve mechanisms to evade or thwart an immune-system response. If pathogens have evolved strategies to avoid triggering an ADP-Hep-mediated immune response, understanding such strategies might suggest new therapeutic approaches to fight bacterial infections.

The authors' observation that host enzymes can convert bacterial metabolites that have poor immune-activating characteristics into potent PAMPs offers a new perspective on the evolutionary battle between pathogens and their hosts. Although Zhou *et al.* show that ADP-Hep is the relevant immune-triggering ligand for *Y. pseudotuberculosis* infections, it remains to be seen whether HBP is converted into ADP-heptose 7-P during other bacterial infections. This issue is particularly relevant for pathogens (for example, *Shigella*) that invade the host-cell cytoplasm and that might shed PAMPs such as HBP directly into the cytoplasm. Zhou and colleagues' work also offers a fresh perspective on the types of molecule that can act as PAMPs or their PRRs, and where and how researchers should be searching for such molecules. ■

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This article was published online on 15 August 2018.

CHEMICAL BIOLOGY

DNA tags light up sugars on proteins

Methods for imaging sugars attached to proteins — the protein glycoforms — are of interest because glycoforms affect protein movement and localization in cells. A versatile approach is now reported that uses DNA as molecular identity tags.

TADASHI SUZUKI

The attachment of sugar molecules to proteins is one of the most common protein modifications, found in all domains of life. Sugars attached to proteins are called glycans, and modulate the physicochemical and physiological properties of the carrier proteins[1]. But tracking and visualizing glycoforms — the specific patterns of sugars attached to a protein — in cells is challenging, particularly if you want to visualize several different glycoforms at once. Writing in *Angewandte Chemie*, Li *et al.*[2] now report a method for doing this that relies on the dynamic interactions of a set of DNA codes.

Since the early 1990s, the use of fluorescent tags as labels for proteins has revolutionized