REVIEWS

Intracellular pattern recognition receptors in the host response

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The innate immune system relies on its capacity to rapidly detect invading pathogenic microbes as foreign and eliminate them. Indeed, Toll-like receptors are a class of membrane receptors that sense extracellular microbes and trigger anti-pathogen signalling cascades. Recently, intracellular microbial sensors have also been identified, including NOD-like receptors and the helicase-domain-containing antiviral proteins RIG-I and MDA5. Some of these cytoplasmic molecules sense microbial, as well as non-microbial, danger signals, but the mechanisms of recognition used by these sensors remain poorly understood. Nonetheless, it is apparent that these proteins are likely to have critical roles in health and disease.

In an environment rich in potentially harmful microbes, survival of the host organism depends on rapidly mounted defence responses. Such protective mechanisms are evolutionarily conserved in all multicellular organisms and are collectively referred to as innate immunity[1]. Unlike adaptive immunity, which is based on millions of lymphoid cell-surface receptors (generated by complex gene rearrangements) that recognize an infinite variety of antigens, the innate immune system is based on a much smaller number of receptors, called pattern recognition receptors (PRRs). For the most part, PRRs recognize conserved molecular patterns that distinguish foreign organisms—viruses, bacteria, fungi and parasites—from cells of their hosts[1]. Such pathogen-associated molecular patterns (PAMPs) include viral nucleic acids, components of bacterial and fungal cell walls, flagellar proteins, and more. However, this detection system is not foolproof and it can also be activated by a variety of normal host proteins and danger signals that are released by dying cells[2]. Inadvertent activation of PRRs by normal host molecules may have an important role in the pathogenesis of various autoimmune and inflammatory diseases[2].

The first family of PRRs studied in detail was the Toll-like receptor (TLR) family[3]. TLRs are classical transmembrane proteins whose ligand-binding domains—composed of leucine-rich repeats (LRRs)—point towards the extracellular milieu or to the topologically equivalent lumen of membrane-enclosed intracellular compartments[4]. Thus, TLRs recognize either extracellular or membrane-encased foreign organisms. In either case, the TLR signal transduction domains, known as Toll/IL-1 receptor (TIR) domains, are directed towards the cytoplasm and transduce their signals through interaction with cytoplasmic adaptor proteins, which also contain TIR domains[4]. Ligand-induced receptor and adaptor dimerization results in recruitment and activation of additional signalling proteins and eventual triggering of a host-defence response, entailing production of antimicrobial peptides, proinflammatory chemokines, and cytokines, antiviral cytokines, adhesion molecules and enzymes that catalyse production of secondary inflammatory mediators and bactericidal molecules. Recently, however, two other families of PRRs were described: the NLRs (NOD-like receptors) and the RLHs (RIG-like helicases). Unlike TLRs, these families consist of soluble proteins that survey the cytoplasm for signs that broadcast the presence of intracellular invaders. This review will focus on recent progress in understanding the function and signalling mechanisms used by cytoplasmic innate immune receptors.

NOD-like receptors, or NLRs

The first intracellular PAMP sensors to be discovered were NOD1 and NOD2 (also known as CARD4 and CARD15, respectively; refs 5, 6). They are members of the emerging NLR family (also known as NOD-LRR, NACHT-LRR and CATERPILLER) implicated in such host defence[7–9]. NLRs contain three distinct domains: an amino-terminal CARD or pyrin effector domain (with the exception of NAIP and possibly NOD5), a nucleotide-binding and oligomerization domain (the so-called 'NACHT' domain), and a variable number of carboxy-terminal LRRs[9] (Fig. 1). NLRs comprise two large sub-classes—the NODs (NOD1–5) and 14 members of the NALP clan[9]. With the IPAF, NAIP and CIITA group of proteins, a total number of 22 NLR members have been identified so far[9]. The biological significance of most of the NLRs remains to be determined.

NLR activation is suggested to be similar to the presumed mechanism described for the structurally related plant resistance genes[10] or Apaf-1 (ref. 11). NLRs are synthesized in an autorepressed, inactive form. Their LRRs are thought to fold back onto the remainder of the protein, thereby blocking NACHT-mediated oligomerization. Specific activation of the sensor platform is triggered through direct or indirect binding of ligands to the LRRs, thereby inducing NACHT-dependent oligomerization and formation of higher-order complexes. Rather than repeat several recent reviews[7–9], the next sections will focus mainly on the function of two NLRs: NOD2 and NALP3 (also called cryopyrin).

The NOD proteins

NOD1 and NOD2 detect bacterial peptidoglycan, and through a CARD-dependent recruitment of RIP2 (refs 12, 13) drive activation of mitogen-activated protein kinases (MAPKs) and NF-κB (Fig. 2). The minimal structural requirement for peptidoglycan-mediated activation of NOD2 is muramyl dipeptide, which is present in both Gram-positive and Gram-negative bacteria[12,14]. Muramyl dipeptide can be released through the action of bacterial hydrolases during cell-wall biosynthesis and remodelling, or after degradation of ingested bacteria by host lysozyme. Exactly how muramyl dipeptide

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finds its way into the cytoplasm is not clear, but a specific transport system may be involved[15]. It is also unknown whether muramyl dipeptide is recognized directly by NOD2 or by another protein that interacts with NOD2. Although the LRRs of NOD2 are required for muramyl-dipeptide-induced signalling[16], it should be noted that direct binding of muramyl dipeptide to NOD2 is yet to be demonstrated. Furthermore, cellular muramyl-dipeptide-binding activities differ in their molecular weight from NOD2 (ref. 7). Thus, NOD2 may use its LRR to interact with the actual muramyl dipeptide receptor. There is evidence that NOD2 mediates innate immunity to *Streptococcus pneumoniae*[17], *Mycobacteria*[18] and *Listeria monocytogenes*[19]. Increased susceptibility to *Listeria* is linked to the impaired expression of a subgroup of intestinal antimicrobial peptides, known as cryptidins, in NOD2-deficient mice[20]. In contrast to NOD2, NOD1 has a more restricted specificity. It detects only meso-diaminopimelic-acid-containing peptidoglycan, which is found in most Gram-negative, but not Gram-positive, bacteria[21].

Much of the recent interest in NOD2 was generated by the association of *NOD2* mutations with two chronic inflammatory disorders: Crohn's disease and Blau syndrome. Crohn's disease is an inflammatory bowel disease characterized by granulomatous inflammation of the distal ileum, associated with increased production of IL-1β and TNFα, and activation of NF-κB, in lamina propria inflammatory cells[22,23]. Almost 50% of familial Crohn's disease cases in Western populations are linked to three *NOD2* mutant alleles: R702W, G908R and L1007fsinsC (refs 24, 25). Homozygosity for either allele increases the risk of Crohn's disease by up to 40-fold, but many patients who are homozygotes for these mutations remain healthy, and even those who develop the disease are asymptomatic for the first 10–15 years of their life[26]. Thus, it is likely that additional factors, both genetic and environmental, act in conjunction with *NOD2* mutations[22]. Two of the mutant alleles—R702W and G908R—specify single amino-acid substitutions within the LRR, whereas the third—L1007fsinsC—results in a frame-shift mutation and removes the last 33 amino acids of the NOD2 polypeptide. Transient expression of NOD2 in non-myeloid cells confers the ability to activate a co-transfected NF-κB reporter construct by exogenous muramyl dipeptide, and using this assay it was concluded that all three Crohn's-disease-linked mutations impair muramyl dipeptide recognition[7]. In addition, cultured macrophages or peripheral blood monocytes from Crohn's disease patients that are homozygous for the *NOD2* mutant alleles also show defects in activation of NF-κB and induction of proinflammatory genes in response to muramyl dipeptide[12,27]. However, these results, which suggest that Crohn's-disease-linked *NOD2* mutations are loss-of-function mutations, are not entirely consistent with the common clinical observations of elevated proinflammatory cytokines and presence of activated NF-κB in the lamina propria of Crohn's disease patients[22,23]. Indeed, the analysis of dendritic cells derived from such patients revealed increased expression of certain inflammatory marker genes including IL-1β upon incubation with muramyl dipeptide[78].

In an attempt to elucidate the functional relationship between *NOD2* mutations and Crohn's disease, two different mouse *Nod2* mutants were generated: one a complete knockout, which no longer expresses the polypeptide[20], and the other a knockin mutant, $Nod2^{2939ic}$, which carries the same mutation as the human L1007fsinsC allele[28]. The latter mouse expresses a normal amount of a truncated NOD2 missing the last 33 amino acids. Both mouse mutants are asymptomatic and do not develop a spontaneous disease. Consistent with the complete absence of NOD2, macrophages from $Nod2^{-/-}$ mice do not produce proinflammatory cytokines or undergo NF-κB activation after muramyl dipeptide challenge[20]. Conversely, $Nod2^{2939ic}$ macrophages show elevated

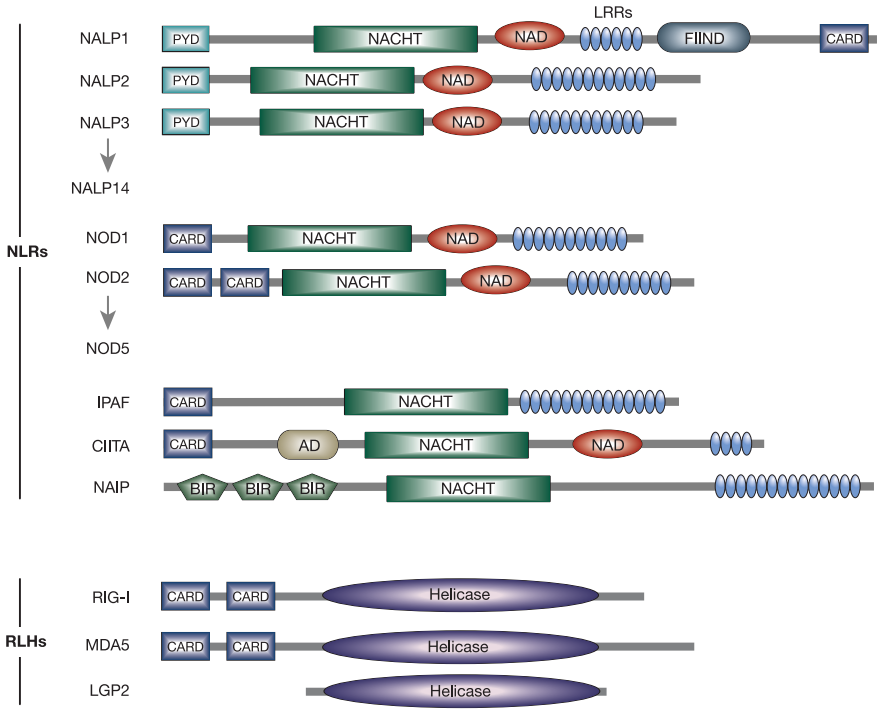

Figure 1 | Intracellular sensors of bacteria, viruses and danger signals. NOD-like receptors (NLRs) are characterized by three distinct domains: the putative ligand-sensing leucine-rich repeats (LRRs); the NACHT domain, which mediates oligomerization; and an effector domain, which can be a pyrin domain (PYD), a CARD (caspase recruitment domain) or a BIR (baculovirus IAP repeat) domain. Most of the NLRs also contain a NACHT-associated domain (NAD). NLRs comprise two large subfamilies: 14 members of the PYD-containing NALP clan and five members of the mostly CARD-containing NODs (NOD5 does not contain a typical CARD domain). The two CARD-containing proteins CIITA and IPAF, and the BIR-containing NAIP protein, constitute the remaining NLR members. RIG-like helicases (RLHs) contain a helicase and two CARD domains, except for LGP2 where the CARDs are absent. Additional abbreviations: FIIND, function to find; AD, activation domain.

responsiveness to muramyl dipeptide, measured by either NF-κB and IKK (IκB kinase) activation or induction of proinflammatory cytokines[28]. However, even in *Nod2*^{2939ic} macrophages the ability of muramyl dipeptide to elicit NF-κB activation or induce the expression of genes encoding proinflammatory cytokines is modest at best, relative to the activity of typical TLR ligands such as LPS (lipopolysaccharide; ligand for TLR4) or polyinosinic:polycytidylic acid (poly(I:C); ligand for TLR3). Given that macrophages and dendritic cells, which specialize in the recognition of pathogens, express many distinct TLRs capable of strong NF-κB activation, it is rather unlikely that the primary signalling function of NOD2 (and probably other NOD proteins) is also NF-κB activation. In other words, given the presence of TLRs that recognize many different microbial PAMPs, it is improbable that the complete absence of NOD2 will generate a 'hole' in the NF-κB activation response, one of the principal effector arms of the host defence system. Notably, macrophages from *Nod2*^{2939ic} mice also show increased IL-1β secretion on muramyl dipeptide stimulation[28]. Furthermore, dendritic cells from Crohn's disease patients that are homozygous for the same mutation show elevated expression of IL-1β mRNA after stimulation with muramyl dipeptide[78]. The results contrast with another report claiming lack of muramyl dipeptide responsiveness in blood monocytes isolated from Crohn's disease patients bearing similar NOD2 mutations[27]. The basis for this discrepancy is yet to be determined.

The NALP3 inflammasome

NALP proteins are characterized by the presence of a N-terminal pyrin effector domain (Fig. 1; for reviews, see refs 7–9). At least some of them have an important role in activation of proinflammatory caspases through formation of a complex called the 'inflammasome'. Two types of NALP inflammasomes were identified[29]. The NALP1 inflammasome composed of NALP1, the adaptor protein ASC, caspase 1 and caspase 5 (ref. 30), and the NALP2/NALP3 inflammasome that contains—in addition to NALP2 or NALP3—CARDINAL, ASC and caspase 1, but not caspase 5 (ref. 31; Fig. 2). Both inflammasomes control the processing and activation of the proinflammatory cytokines IL-1β and IL-18.

What are the signals activating the NALP3 inflammasome? It seems that not only PAMPs but also the presence of host danger signals (danger-associated molecular patterns, or DAMPs) can be sensed by inflammasomes. Low concentrations of intracellular potassium ($[K^+] < 70$ mM) seems to be the common denominator of an acute cellular stress triggering inflammasome activation[30]. For example, massive K^+ efflux occurs when high concentrations of ATP (5 mM) activate the purinergic $P2X_7$ receptor[32]. Potassium-channel-forming bacterial toxins such as *Staphylococcus aureus* α-toxin or gramicidin from *Bacillus brevis* also activate the inflammasome in a K^+-dependent manner[32,33]. Thus, the inflammasome does not only sense the presence of bacterial components (see below), but is also endowed with the ability to detect non-microbial danger signals.

In 1994, Matzinger proposed a new concept suggesting that endogenous factors released from tissues undergoing destruction alert the immune system through direct activation of dendritic cells without exposure to foreign substances[34]. Several groups subsequently showed that necrotic cell lysates are a source of endogenous factors that induce dendritic cell activation. One of the components that meets the criteria of an endogenous danger signal is crystalline

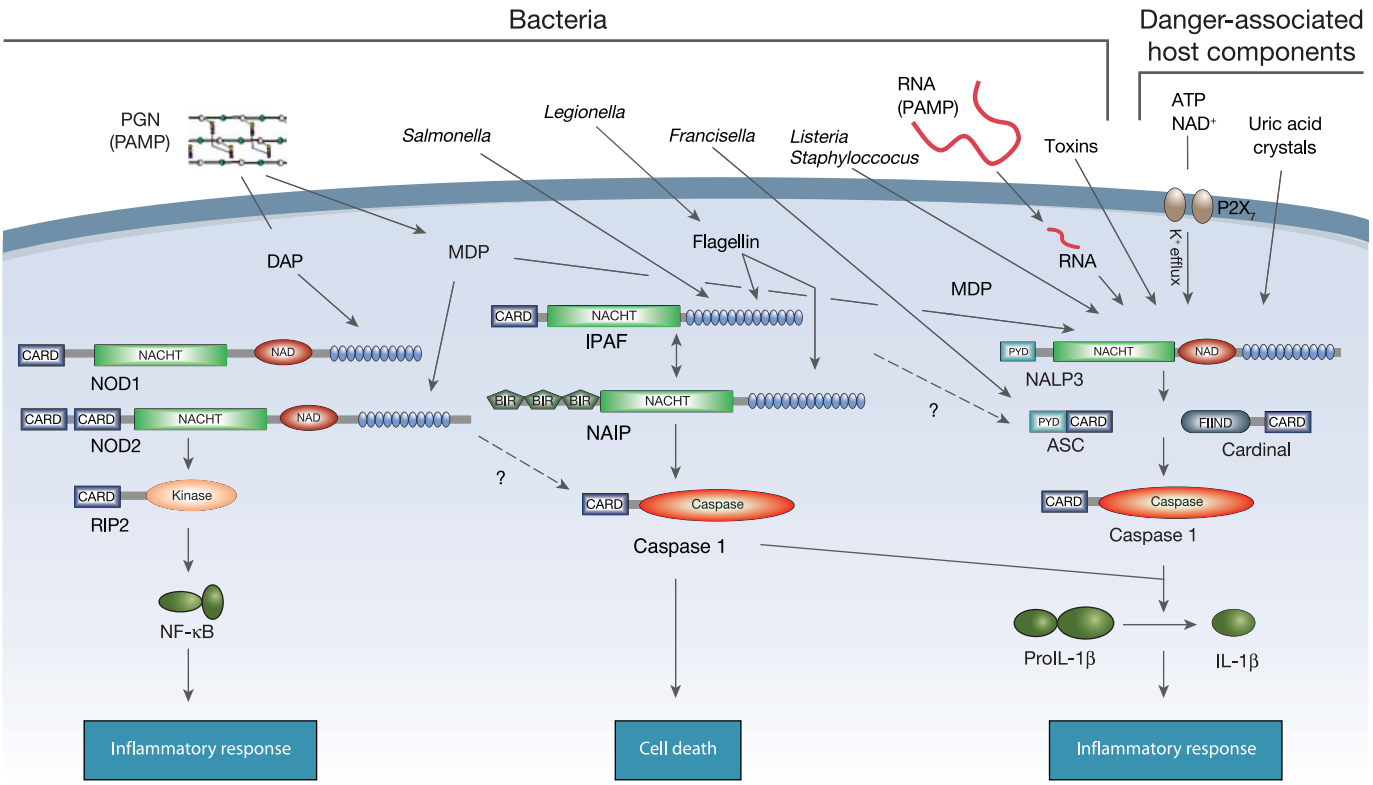

Figure 2 | Activation of NLRs by bacterial and host-derived components. On recognition of peptidoglycan (PGN)-derived molecules (meso-diaminopimelic acid (DAP) and muramyl dipeptide (MDP), respectively), NOD1 and NOD2 recruit RIP2, which, in turn, activates NF-κB. NOD2 activation can lead to caspase 1 activation through a mechanism that remains to be identified. Muramyl dipeptide (and bacterial RNA) also activates the NALP3 inflammasome, which is formed by NALP3, Cardinal, ASC and caspase 1, resulting in the processing of proIL-1β. Endogenous danger signals that activate NALP3 include uric acid crystals and the efflux of K^+, triggered by ATP, NAD^+ or bacterial toxins. Various bacteria trigger activation of distinct NLR pathways. Whereas caspase 1 activation by *Salmonella* and *Legionella* requires IPAF, NAIP (and ASC), but not NALP3, *Listeria* and *Staphylococcus* triggers caspase 1 activation via the NALP3 inflammasome.

monosodium urate[35]. Uric acid is normally present in tissues as a degradation product of purines. Under stress conditions, monosodium urate may be released to eventually form crystals that alert dendritic cells and other immune cells such as macrophages. Although the adjuvant effect of monosodium urate can be advantageous by triggering a potent innate immune response against pathogens, it can also trigger deleterious autoinflammatory responses. Indeed, monosodium urate is recognized as the aetiological agent of gout, a condition in which elevated uric acid is associated with the onset of arthritis. Notably, not only monosodium urate but also calcium pyrophosphate dihydrate crystals—involved in the arthropathy pseudogout—were recently shown to activate the NALP3 inflammasome[36]. Despite the existence of 14 NALPs, all host danger signals tested so far, including those that lower intracellular K^+ concentration, seem to activate caspase 1 through the NALP3 inflammasome[36–38]. This suggests that NALP3 may represent one of the long-sought host danger receptors.

In addition to DAMPs, NALP3 also senses bacterial PAMPs. Interestingly, NALP3 was proposed to detect the same PAMPs—namely peptidoglycan and its degradation product muramyl dipeptide[39]—that activate NOD2, suggesting that these bacterial cell wall components are predominantly sensed by the cytoplasmic NLRs and not extracellular TLRs (the reported peptidoglycan–TLR2 interaction was recently questioned[40]). Moreover, bacterial RNA and small antiviral compounds were also proposed to activate the NALP3 inflammasome independently of TLRs[41], suggesting that multiple PAMPs may activate the NALP3 inflammasome. However, the physiological relevance of muramyl dipeptide and bacterial RNA detection by NALP3 remains to be addressed *in vivo*. It is known that not all bacteria are sensed by the NALP3 inflammasome despite the presence of peptidoglycan in their cell walls. Whereas *L. monocytogenes* and *S. aureus* do not elicit caspase 1 activation in *Nalp3*$^{-/-}$ and *Asc*$^{-/-}$ mice, caspase 1 activation mediated by *Francisella tularensis* requires ASC but not NALP3 (ref. 37), suggesting that NALP3- independent sensing occurs. Similarly, *Salmonella-typhimurium*-induced inflammatory response and caspase-1-dependent cell death are ASC-dependent, but not NALP3-dependent[37,38]. Intriguingly, in addition to ASC, *Salmonella*-induced IL-1β processing and cell death also require IPAF[42]—a member of the NLR family that was shown to be activated by intracellular bacterial flagellin[43,44] and that can directly activate caspase 1 without the need of the ASC adaptor. This suggests that *Salmonella* sensing requires a special conduit, provided by IPAF, in order to activate a putative NALPX (ASC-dependent) inflammasome.

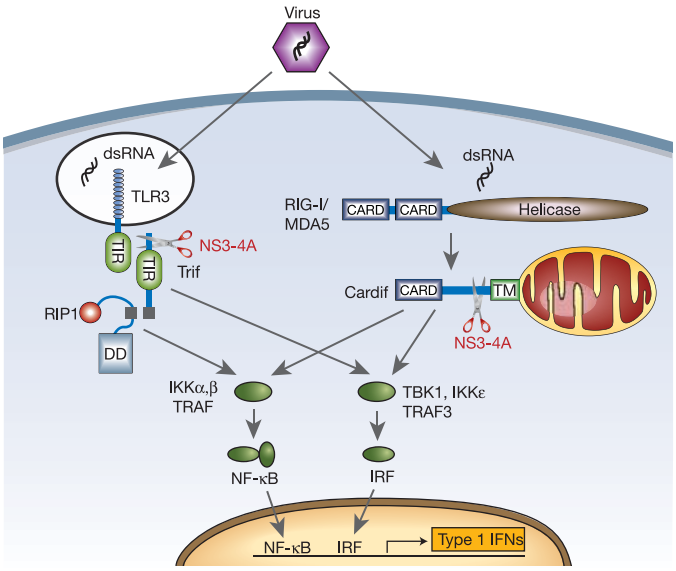

Figure 3 | Sensing of viral dsRNA by TLR3 and RLH. Left: On dsRNA binding within endosomes, TLR3 recruits the adaptor Trif through a TIR–TIR interaction. Trif, in turn, recruits RIP1 to activate NF-κB, via TRAFs and the IKK (IκB kinase) complex. Trif also recruits TBK1/IKKε and TRAF3 to activate IRF3/7. Right: On dsRNA binding, RIG-I (and also MDA5) recruits mitochondrially anchored Cardif, which, in turn, recruits appropriate IKKs to activate NF-κB and IRF, resulting in the induction of type I IFN. During an HCV infection, both Trif and Cardif are cleaved and inactivated by the HCV NS3-4A protease. Additional abbreviations: DD, death domain; TIR, Toll/IL-1 receptor; TM, transmembrane region.

Owing to its potentially dangerous proinflammatory action, the synthesis, processing and release of IL-1β by macrophages are tightly controlled and require at least two distinct stimuli[45]. An inflammatory stimulus, given by TLR ligands such as LPS, induces accumulation of large intracellular stores of the 31-kDa proIL-1β (step 1), while a second stimulus activates the inflammasome and caspase 1 (step 2) followed by release of the active mature 17-kDa IL-1β (step 3). The second and third stimuli can be provided by DAMPs such as ATP, NAD^+, nigericin, bacterial toxins (K^+ efflux) or uric acid crystals[36,41,46,47]. Although TLR activation was proposed to support all three steps[41], this seems to be quite inefficient as it was not observed by others[32,33,36,37,42]. This 'three-step' model may guarantee that initiation of innate immune defence requires not only a signal from the extracellular milieu via TLRs, but, in addition, a host danger signal, thereby ensuring that innate immunity is not accidentally triggered by, for example, commensal bacteria.

The crucial role of the NALP3 inflammasome has not only been highlighted by analysis of inflammasome-deficient mice[36–38,41,42,48], but also by the identification of NALP3 mutations associated with three autoinflammatory disorders: Muckle–Wells syndrome, familial cold autoinflammatory syndrome, and neonatal-onset multisystemic inflammatory disease[49,50]. These disorders are associated with constitutive release of IL-1β from monocytes of patients, suggesting that the mutations trigger spontaneous NALP3 oligomerization without the need of a ligand[31]. Importantly, patients with NALP3 mutations are now being treated with the IL-1R antagonist ILra (anakinra)[51]. The treatment leads to an almost immediate relief from all symptoms including rashes, periodic fever and arthritis[52–54].

Little is known about the role of most of the remaining NLRs in innate immunity, as the corresponding knockout mice are not yet available. One exception is NAIP, where genetic studies in mice revealed that NAIP5 is involved in caspase-1-dependent susceptibility of macrophages to *Legionella pneumophila*[55] through sensing of flagellin[56–58]. IPAF is also required for *L. pneumophila* growth restriction[57], which is explainable by the observation that NAIP5 and IPAF physically interact[57]. *Legionella*-induced IL-1β release, but not bacterial growth, is restricted in ASC-deficient macrophages[42,57], suggesting that NAIP has an antibacterial role that is independent of the NALP inflammasome.

RIG-like helicases, or RLHs

Innate immune responses against invading viruses also rely on detection of viral PAMPs and subsequent production of antiviral cytokines such as type-I interferons (IFNs). One prototypical viral PAMP is double-stranded (ds)RNA, which can be detected by TLR3 (ref. 59). Although TLR3 was the first reported dsRNA receptor capable of signalling to IRF and NF-κB—two essential transcription factors that regulate type-I IFN production (Fig. 3)—its role as the primary antiviral receptor was recently challenged. *In vivo* antiviral responses to several viruses, including vesicular stomatitis virus (VSV), lymphocytic choriomeningitis virus (LCMV), reovirus, and murine cytomegalovirus (MCMV), were found to be similar between TLR3-deficient and wild-type mice[60]. Even *in vitro* responses to synthetic dsRNA are rendered TLR3-independent once cells are incubated with sufficient levels of synthetic dsRNA[59].

Hence, other crucial dsRNA sensors may exist. Recently, three homologous DExD/H box RNA helicases were identified as cyto-

plasmic sensors of virally derived dsRNA (members of the RLHs). Two family members, retinoic-acid-inducible gene I (RIG-I; also called DDX58) and melanoma-differentiation-associated gene 5 (MDA5; also called Helicard), share two N-terminal CARDs followed by an RNA helicase domain (Fig. 1). When activated during a viral infection, dsRNA stimulation or upon overexpression in cells, RIG-I and MDA5 trigger activation of NF-κB and IRF3/7, which cooperate in induction of antiviral type I IFN[61,62] (Fig. 3). The third helicase, LGP2, is devoid of CARDs and prevents activation of antiviral responses, most likely through sequestration of dsRNA from RIG-I or MDA5 (refs 63, 64). Of note, other cytoplasmic dsRNA-binding proteins (such as PKR and 2′,5′-oligoadenylate synthetase) also constitute important antiviral molecules, however they act in a second, IFN-dependent phase[65].

The *in vivo* relevance of RIG-I and MDA5 was addressed through generation of knockout mice, which show impaired antiviral responses against different viruses. RIG-I, but not MDA5, mounts antiviral responses against the positive-strand single-stranded (ss)RNA virus Japanese encephalitis virus, and a set of negative-strand ssRNA viruses such as Newcastle disease virus, VSV, Sendai virus and influenza virus. In contrast, MDA5 senses the presence of the positive-strand ssRNA picornavirus encephalomyocarditis virus[66,67]. Interestingly, although antiviral responses are strongly affected in conventional dendritic cells and mouse embryonic fibroblasts derived from RIG-I-deficient animals, no difference compared to wild-type counterparts is observed in plasmacytoid dendritic cells, which instead require the TIR-containing TLR adaptor MyD88 and probably TLR7 and/or TLR9, which also recognize viral nucleic acids, to mount antiviral responses[66].

Mechanistically, RIG-I and MDA5 use their CARDs to signal downstream events, which suggest the existence of (a) putative CARD adaptor molecule(s). Such an adaptor was recently identified, and named CARD adaptor inducing IFN-β (Cardif; also called MAVS, IPS-1 or VISA)[68–71]. Cardif contains a N-terminal CARD that interacts with both RIG-I and MDA5, whereas its C terminus harbours a transmembrane region that targets Cardif to the outer mitochondrial membrane[69] (Fig. 3). Hence, both RIG-I and MDA5 signalling converge at Cardif, a hypothesis that was confirmed with the recent generation of Cardif-deficient mice[72]. Notably, when Cardif is released from mitochondria to the cytoplasm, or is targeted to another organelle such as the endoplasmic reticulum, it no longer mediates downstream IRF and NF-κB activation[69]. The relevance of Cardif as a crucial antiviral molecule is also inferred from experiments that showed Cardif cleavage and inactivation during hepatitis C virus (HCV) infection[68,73]. Further, the TLR3 adaptor Trif is targeted by the same HCV viral protease (NS3-4A), which also results in its inactivation[74]. Hence, the development of small antiviral compounds targeting NS3-4A, which is also indispensable for HCV maturation, is an attractive strategy for treatment of HCV infections[75]. Once activated by dsRNA, the Cardif platform most probably recruits appropriate signalling intermediates, such as IKKs (namely IKKα, β, ε and TBK1) to activate NF-κB and IRF transcription factors[68–71]. Furthermore, TRAF3, a unique antiviral TRAF molecule implicated in type I IFN production, may also participate in these intracellular events[76,77]. Undoubtedly, future research will aim at understanding the molecular mechanisms of antiviral pathways that emanate from the recently described RLH family, and how viruses counteract them.

Concluding remarks

A growing number of receptors/sensors for intracellular pathogens and endogenous danger signals are currently being discovered. During microbial infection, these receptors are activated by PAMPs and alert the immune system to take the necessary countermeasures. If infection results in cell damage, endogenous activators are released (such as crystalline uric acid), setting the stage for an optimal immune response. Many questions concerning how these receptors distinguish between pathogenic and commensal bacteria, and between danger signals and normal cellular constituents, remain unanswered. For example, how does RIG-I undergo activation only when RNA originates from viruses and not from cellular RNA. It seems that the proper transient activation of NLR responses is difficult to sustain and is easily disrupted, leading to various inflammatory diseases. Identification of these novel sensors and their signalling mechanisms may therefore provide us with new targets for the development of drugs for treating such poorly understood diseases. The therapeutic potential that this new insight provides is most dramatically exemplified by the success of IL-1ra in treating hereditary inflammatory disorders.

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