NOD-LIKE RECEPTORS (NLRs)

Introduction

In mammals, germ-line encoded pattern recognition receptors (PRRs) detect the presence of pathogens either directly through recognition of pathogen-associated molecular patterns (PAMPs) or indirectly through sensing host-derived danger signals (DAMPs). The innate immune system comprises several classes of PRRs that allow the early detection of pathogens at the site of infection. The membrane-bound toll-like receptors (TLRs) detect microbes on the cell surface and in endosomes. The RIG-1 (retinoic acid-inducible gene I)-like receptors (RLRs; RLHs) and the Nod-like receptors (NLRs; nucleotide-binding domain leucine-rich repeat containing receptors) detect microbial components in the cytosol.

NLR Proteins

The intracellular NLR proteins organize signaling complexes such as inflammasomes and NOD signalosomes. These proteins have been first identified due to their homology with the plant R proteins, a large family of proteins involved in resistance to phytopathogens. NLRs contain three characteristic domains:

1. a C-terminal leucine-rich repeat (LRR) domain responsible for ligand sensing and autoregulation;
2. a central NACHT (NOD) domain that has similarity to the NB-ARC motif of the apoptotic mediator APAF1 and is required for nucleotide binding and self-oligomerization; and
3. an N-terminal effector domain responsible for signal transduction and activation of the inflammatory response. To date, four different N-terminal domains have been identified: acidic transactivation domain, caspase-recruitment domain (CARD), pyrin domain (PYD), and baculoviral inhibitory repeat (BIR)-like domain.

![Diagram of NLR proteins and their domains](www.enzolifesciences.com)

**FIGURE 1:** Human NLRs and their domains.
In 2008, J.P. Ting, et al. proposed a unified standard nomenclature for the NLR gene family based on the N-terminal effector domain (see Table 1).

<table>
<thead>
<tr>
<th>Approved Name</th>
<th>Other Names and Aliases</th>
<th>NLR Family</th>
<th>Domain Organization</th>
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<tr>
<td>CIITA</td>
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<td>NLR family member X1</td>
<td>NOD9; CLR11.3</td>
<td>NLRX</td>
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**TABLE 1:** New standard nomenclature for the human NLR family members.

The following abbreviations are used: AD, acidic activation domain; CARD, caspase activating and recruitment domain; LRR, leucine-rich repeat; NACHT, domain present in NAIP, CIITA, HET-E, and TP-1; BIR, baculovirus inhibitor of apoptosis repeat; PYD, pyrin domain; NAD, NACHT-associated domain.


**Selected Latest Review Articles**

- Linking inflammasome activation and phagosome maturation: V. Lazarevic & F. Martinon; Cell Host Microbe 3, 199 (2008)
- The microbial and danger signals that activate Nod-like receptors: S. Benko, et al.; Cytokine 43, 368 (2008)
- The role of NLRs and TLRs in the activation of the inflammasome: M.G. Netea, et al.; Expert Opin. Biol. Ther. 8, 1867 (2008)

**Latest Insight**

**T cells regulate innate immune responses through inhibition of NLRP1 and NLRP3 inflammasomes**

A tight regulation of the inflammatory response is essential to avoid tissue damage and related diseases such as arthritis and diabetes type 2. Jürg Tschopp and colleagues examined the role of T cells in the regulation of innate immune responses. They showed that mouse effector and memory CD4+ T cells abolish macrophage inflammasome-mediated caspase-1 activation and subsequent IL-1β release.

Nod Signalosomes

Nod1 (CARD4; NLRC1) and Nod2 (CARD15; NLRC2) are intracellular pattern-recognition molecules (PRMs) of the NLR (Nod-like receptor) family. Nod1 is ubiquitously expressed, while Nod2 expression is restricted to monocytes, macrophages, dendritic cells and intestinal Paneth cells. Both proteins are implicated in the detection of bacterial peptidoglycan (PGN). Nod1 senses mesodiaminopimelic acid (meso-DAP)-containing peptidoglycan found in the cell wall of Gram-negative bacteria. Nod2 seems to be a general sensor which is activated by muramyl dipeptide (MDP), the minimal motif common to all PGNs of Gram-negative as well as Gram-positive bacteria. Upon activation, Nod1 and Nod2 initiate a pro-inflammatory response through recruitment of the receptor-interacting protein 2 (RIP-2; RICK; CARDIAK). K63-linked ubiquitination of NEMO ultimately leads to the recruitment of TAK1 and the IKK complex. The interaction between RICK and NEMO ultimately leads to the activation of IKKs and NF-κB by TAK1 (see Figure 2). Both Nod1 and Nod2 are key receptors in epithelial cells where they control infections via the gastro-intestinal system. Mutations in Nod1 have been reported to confer susceptibility to several inflammatory disorders including inflammatory bowel disease, atopic eczema and asthma. Similarly, mutations in Nod2 have been linked to Crohn’s disease.

**Nod1 [CARD4] & Nod2 [CARD15]**

**Nod1 (human), pAb (AL184)**

ALX-210-918-C050

From rabbit. IMMUNOGEN: Synthetic peptide corresponding to aa 2-31 (EEOGHESEMIPSEPHQIIKSKRELLV) of human Nod1 (CARD4). SPECIFICITY: Recognizes human Nod1. APPLICATION: WB.

**Nod2 (human), mAb (2D9)**

ALX-803-307-1


**Nod2 (human), pAb**

ALX-210-373-1


**RIP2 [RICK]**

**RIP2 (human), mAb (Nick-1)**

ALX-804-139-C100


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**Latest Insight**

**A new role for Nod2 in antiviral immunity**

Recent studies identified a second pathway of Nod2 activation through viral ssRNA. A. Sabbah, et al. showed that ssRNA viruses activate Nod2 and subsequently lead to the production of interferon and anti-viral immunity. This response requires MAVS, a mitochondrial membrane-anchored CARD protein that is a potent activator of IRF3.

Inflammases

By definition, an inflammasome represents a high molecular weight complex that activates inflammatory caspases and the cytokines of the IL-1 family. Several inflammasomes have been described and are defined by the NLR protein that they contain: the NLRP1 (NALP1) inflammasome, the NLRP3 (NALP3) inflammasome and the NLRC4 (IPAF) inflammasome. Inflammasomes can be activated through multiple signals including live bacteria, microbial molecular patterns, microbial toxins, xenocompounds and endogenous danger signals (for a complete overview see Page 6). Upon sensing of their respective ligands, NLPR1 and NLPR3 recruit the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) through homophilic PYD-PYD interactions. ASC contains an N-terminal PYD and a C-terminal CARD that allows the recruitment of inflammatory caspases through CARD-CARD interactions. The oligomerization of NLRPs is believed to bring inflammatory caspases into close proximity, leading to their activation within the inflammasome. In contrast, NLRC4 does not recruit an adaptor molecule but directly activates caspase-1 via its CARD domain (see Figure 3).

The assembly of the different inflammasomes leads to a common outcome, namely the activation of an inflammatory caspase. In mammals, these include human and mouse caspase-1 and -14, human caspase-4 and -5 as well as mouse caspase-12. These caspases all have a CARD domain followed by a domain containing the catalytic residue and are called inflammatory caspases because their main substrates are cytokines (such as IL-1β, IL-18 and possibly IL-33). IL-1β are cleaved by caspase-1 to yield IL-1β (inactive form) and IL-1β (active form). These caspases all have a CARD domain followed by a domain containing the catalytic residue and are called inflammatory caspases because their main substrates are cytokines (such as IL-1β, IL-18 and possibly IL-33). IL-1β are cleaved by caspase-1 to yield IL-1β (inactive form) and IL-1β (active form).

Inflammasomes in infection and inflammation, and promotion of cell survival through activation of caspase-1 and -14 have been implicated in transducing the signal from the membrane to the NLRP3 inflammasome. Crystals, that are too large to be internalized, remain at the cell surface where they induce membrane perturbations or “frustrated phagocytosis”. Reactive oxygen species (ROS), produced through the actions of membrane-bound NADPH oxidase, are implicated in transducing the signal from the membrane to the NLRP3 inflammasome. Inflammasome assembly stimulates the activity of caspase-1, which mediates processing of cytokines, glycolysis enzymes and other substrates, pyroptosis, unconventional protein secretion, and promotion of cell survival through activation of SREBPs in response to pore-forming toxins.
**Antibodies to NALPs / NLRPs**

**NALP1 (human), mAb (Nalpy1-4)**

ALX-804-803-C100 100 µg


**FIGURE:** Immunofluorescence microscopy showing the detection of endogenous NALP3 in THP1 cells with the NALP3 (human), mAb (Nalpy3-a) (Prod. No. ALX-804-818). Method: Following fixation with paraformaldehyde 3.7%, THP1 cells were incubated with the NALP3 (human), mAb (Nalpy3-a) (Prod. No. ALX-804-818) at a 1:100 dilution. An anti-mouse IgG antibody conjugated with Alexa Fluor 488 was used for detection.

**NALP1 (human) (CT), pAb (Bur 242)**

ALX-210-017-R050 50 µl

From rabbit. IMMUNOGEN: Synthetic peptide corresponding to aa 2-25 (AGGWGRALCYHELKKEELKEFO) of N-terminal human NALP1 (NACHT-, LRR- and PYD-containing protein 1). SPECIFICITY: Recognizes human NALP1. APPLICATION: WB.

**NALP1 (human) (NT), pAb (Bur 241)**

ALX-210-018-R050 50 µl

From rabbit. IMMUNOGEN: Synthetic peptide corresponding to aa 161-180 (G2RARDAILDALENLTAEELKKFKLKL27) of N-terminal human NALP1 (NACHT-, LRR- and PYD-containing protein 1). SPECIFICITY: Recognizes human NALP1. APPLICATION: IHC (FS, PS), ICC, IP, WB.

**NALP3 (human), mAb (Nalpy3-a)**

ALX-804-818-C100 100 µg


**FIGURE:** Staining of endogenous NALP3 in epithelial layer of human tonsil (frozen section) using NALP3 (human), mAb (Nalpy3-b) (Prod. No. ALX-804-819).

**NALP3 (human), mAb (Nalpy3-b)**

ALX-804-819-C100 100 µg


**IPAF [CARD12]**

**IPAF (human), mAb (Luna-1)**

ALX-804-848-C100 100 µg


**Pyrin**

**Pyrin (human), pAb (AL196)**

ALX-210-946-C100 100 µg

From rabbit. IMMUNOGEN: Synthetic peptide corresponding to aa 2-29 (A7K-TPSDHLSTLVEPVDPFKFKKLQ) of human pyrin (MEFV; mediterranean fever protein). SPECIFICITY: Recognizes human pyrin. APPLICATION: IB, WB.

**Asc**

**Asc, pAb (AL177)**

ALX-210-905-R100 100 µg

From rabbit. IMMUNOGEN: Synthetic peptide corresponding to aa 2-161 (TPRIPDDLTPSHSSPAGQPQLKDQDD) of N-terminal human Asc (apoptosis-associated speck-like protein containing CARD; Pycard). SPECIFICITY: Recognizes human and mouse Asc. APPLICATION: ICC, IP, WB.

**IPAF (human), mAb (Luna-1)**

ALX-804-848-C100 100 µg


**Pyrin**

**Pyrin (human), pAb (AL196)**

ALX-210-946-C100 100 µg

From rabbit. IMMUNOGEN: Synthetic peptide corresponding to aa 2-29 (A7K-TPSDHLSTLVEPVDPFKFKKLQ) of human pyrin (MEFV; mediterranean fever protein). SPECIFICITY: Recognizes human pyrin. APPLICATION: IB, WB.
## Nod-like Receptors & Their Ligands

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<th>NLR</th>
<th>Elicitor</th>
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<tr>
<td><strong>INOD1</strong></td>
<td>Microbial motifs: meso-Lanthionine, meso-DAP</td>
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<td>γ-D-Glu-meso-DAP (E-DAP)</td>
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<td>L-Ala-γ-D-Glu-meso-DAP (TrpDAP)</td>
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<td>D-Lactyl-L-Ala-γ-D-Glu-meso-DAP-Gly (FK158)</td>
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<td>Bacterial extracts</td>
<td>Bacillus species, B. anthracis spores, L. pneumophila, S. typhimurium, M. tuberculosis</td>
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<td>Live bacteria</td>
<td>S. flexneri (G– Intra Ep), K. pyolyticus (γ-D-Glu, S. Typhimurium), Pseudomonas species (G– Intra Ep, F), Chlamydia species (G– Intra Ep, En, F), L. monocytophages (G– Intra Ep, En)</td>
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<td>ALX-746-021</td>
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<td>Live bacteria</td>
<td>L. pneumophila (G– Intra Ep M)</td>
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a) Bacillus species: cereus, simplex, subtilis, megaterium, pumilus.  
b) Pseudomonas species: aeruginosa, putida.  
c) Chlamydia species: pneumoniae, trachomatis, muridarum.  
d) Lactobacillus species: plantarum, pentosus.  
e) Pseudomonas species: aeruginosa, putida.
**Nod-like Receptor Ligands**

**Ac-muramyl-Ala-D-Glu-amide**
[MDP-LD; N-Acetylmuramyl-L-alanyl-D-isoglutamine]

- ALX-151-035-M001 1 mg
- ALX-151-035-M005 5 mg

Synthetic. Specific ligand for NLRP3 (NALP3). For inactive control compound see MDP-DD (Prod. No. ALX-151-036).

**Adenosine 5’-triphosphate . 2Na**

- ALX-480-021-G001 1 g
- ALX-480-021-G005 5 g

Specially crystallized and tested on biological activity.

**Flagellin (high purity)**

- ALX-522-058-C010 10 µg

Isolated from *Salmonella typhimurium* strain 14028. Binds to human and mouse TLR5 (Toll-like receptor 5). Activates the NLRC4 (IPAF) inflammasome.

**Imiquimod**

- ALX-420-039-M100 100 mg
- ALX-420-039-M250 250 mg

NLRP3 (NALP3) inflammasome activator.

**Monosodium urate (crystals)**

- ALX-400-047-M002 2 mg

NALP3 inflammasome activator. Specially crystallized and tested on biological activity.

**Valinomycin**

- BML-C1400-0005 25 mg

Isolated from *Streptomyces fulvissimus*. Potassium ionophore. Activates the NLRP3 (NALP3) inflammasome.

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### Latest Insight

Recently, H. Li, et al. reported that 7BIO (7-bromoidrinurbin-3'-oxime), a potent inducer of caspase-independent necrosis, activates the inflammasome and triggers the release of the proinflammatory cytokines IL-1β and IL-18.

- **7BIO**
  - ALX-430-149-M005 5 mg
  - ALX-430-149-M025 25 mg

**R-848**

- ALX-420-038-M005 5 mg
- ALX-420-038-M025 25 mg

Selective ligand for Toll-like receptor 7 (TLR7) in mouse and for TLR7 and TLR8 in human. NLRP3 (NALP3) inflammasome activator.

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For a comprehensive bibliography please visit our website.
**AIM2 – An Inflammasome Sensing Cytoplasmic DNA**

In 2008, D.A. Muruve, et al. reported that the inflammasome recognizes cytosolic microbial and host DNA and triggers an inflammatory response [1]. Four new reports now identified the HIN-200 family member AIM2 (absent in melanoma 2) as a sensor of double-stranded cytoplasmic DNA [2-5]. Their results suggest that AIM2 directly binds to cytoplasmic DNA, triggers the assembly of an AIM2 inflammasome, and results in caspase-1 activation. In addition cytoplasmic DNA also triggers the activation of the apoptotic caspase-3 in an AIM2 dependent way [5].

**Poly(dA:dT) (endotoxin-free) (synthetic)**

[Poly(deoxyadenosine:deoxythymidine) (endotoxin-free) (synthetic)]

ALX-746-022-C050 50 µg

Synthetic. Potent inducer of IFN-α/β. AIM2 inflammasome activator.

**Oligo(dA:dT) (endotoxin-free) (synthetic)**

[Oligo(deoxyadenosine:deoxythymidine) (endotoxin-free) (synthetic)]

ALX-746-023-C050 50 µg

Synthetic. Potent inducer of IFN-α/β.

**Inflammasomes – Related Caspases**

**Caspase-1 (human) (rec.)**

BML-SE168-5000 5000 U

Produced in *E. coli.*

**Caspase-5 (human) (rec.)**

BML-SE171-5000 5000 U

Produced in *E. coli.*

**Caspase-1 Assay Kit for Drug Discovery**

BML-AK701-0001 1 Kit

INCLUDES BOTH COLORIMETRIC AND FLUOROGENIC SUBSTRATES! This kit is a complete assay system to measure protease activity of recombinant caspase-1. Cleavage of a tetrapeptide substrate is monitored colorimetrically at 405 nm or fluorometrically (Ex. 360 nm/Em. 460 nm). Assays are performed in a convenient 96-well plate format. QUANTITY: 96 assays.

**LIT:**


**FIGURE 5:** AIM2 inflammasome.

The HIN200 family member AIM2 binds DNA via its HIN200 domain. The oligomerization of the protein with the adaptor ASC recruits pro-caspase-1 via a homotypic CARD interaction to form the AIM2 inflammasome. Activated caspase-1 mediates processing and secretion of pro-IL-1β and pro-IL-18 in addition to triggering pyroptosis.

Adapted from: The innate immune response to DNA: A. Vilaysane & D.A. Muruve; Semin. Immunol. 21, 208 (2009)