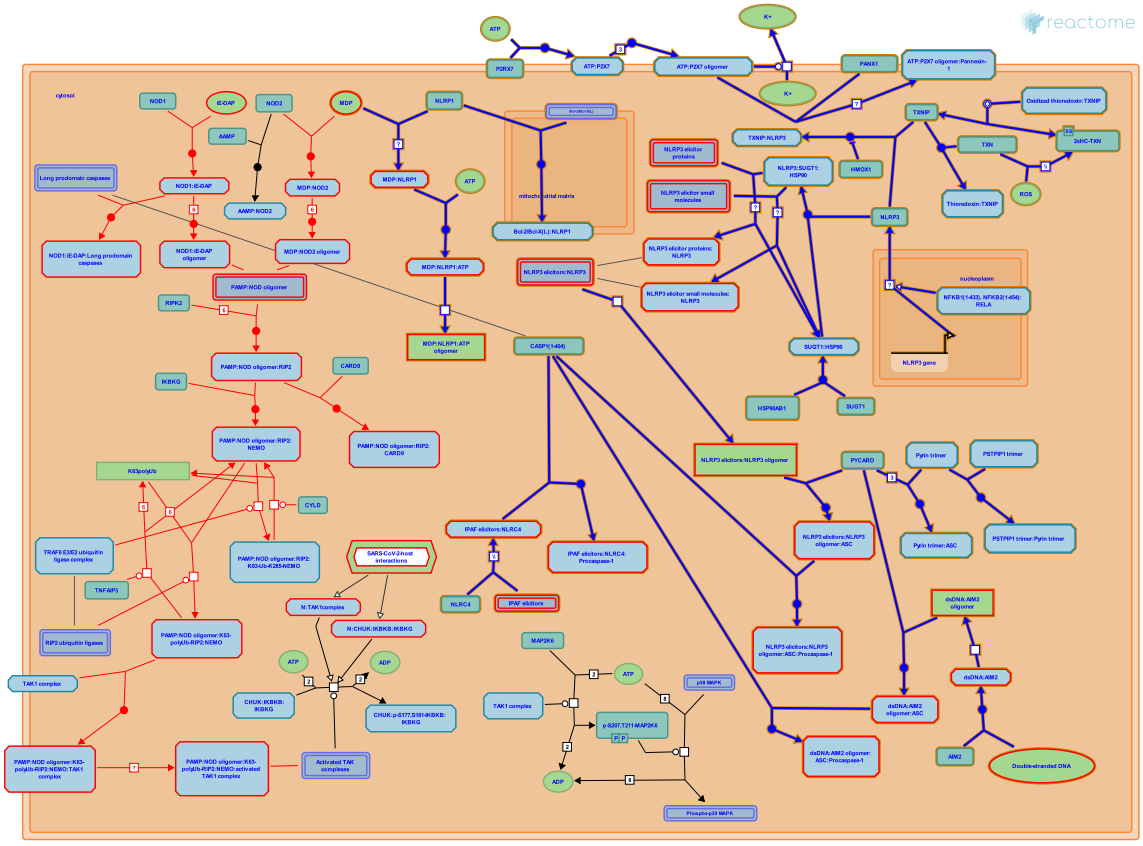
# Inflammasomes



Jupe, S., Kufer, TA., Rittinger, K., Wong, E.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

19/05/2024

# Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

## Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

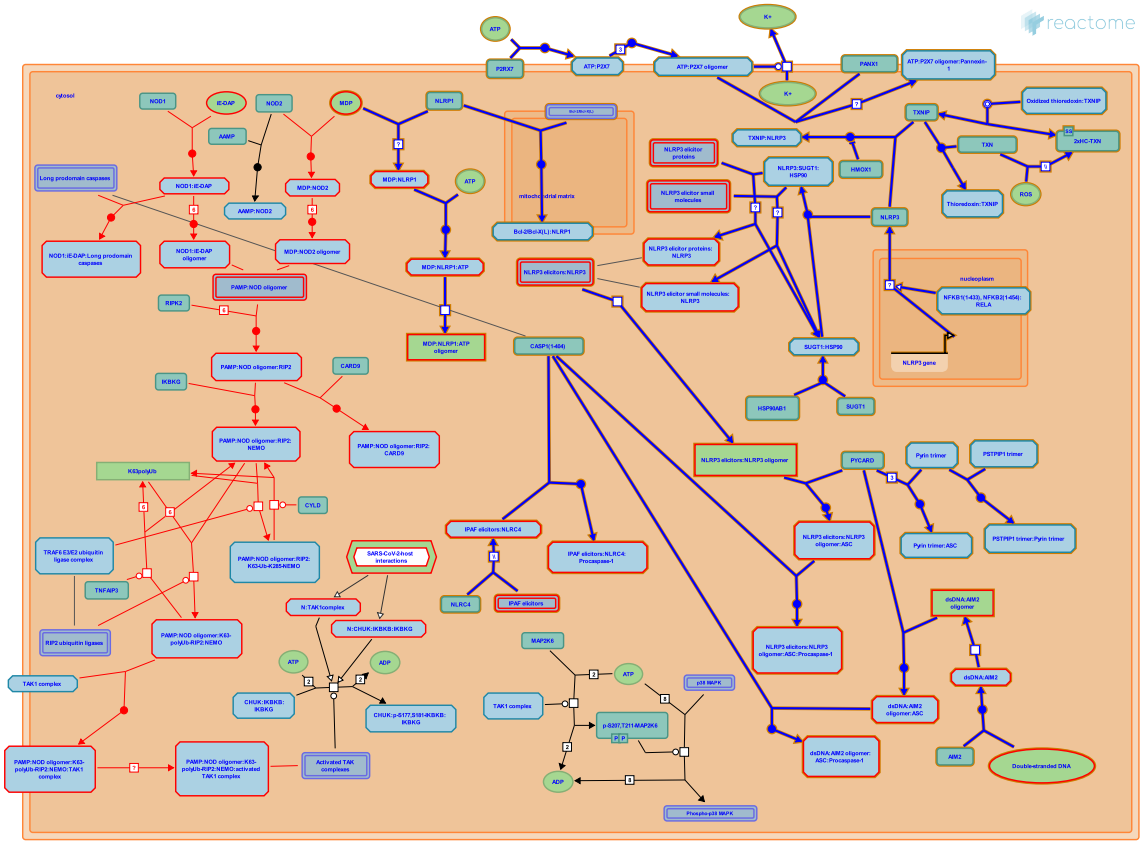
Reactome database release: 88

This document contains 5 pathways (see Table of Contents)

## Inflammasomes ↗

**Stable identifier:** R-HSA-622312

**Compartments:** cytosol




In contrast to NOD1/2 some NLRPs function as large macromolecular complexes called 'Inflammasomes'. These multiprotein platforms control activation of the cysteinyl aspartate protease caspase-1 and thereby the subsequent cleavage of pro-interleukin 1B (pro-IL1B) into the active proinflammatory cytokine IL1B. Activation of caspase-1 is essential for production of IL1B and IL18, which respectively bind and activate the IL1 receptor (IL1R) and IL18 receptor (IL18R) complexes. IL1R and IL18R activate NFkappaB and other signaling cascades.

As the activation of inflammasomes leads to caspase-1 activation, inflammasomes can be considered an upstream step of the IL1R and IL18R signaling cascades, linking intracellular pathogen sensing to immune response pathways mediated by Toll-Like Receptors (TLRs). Monocytes and macrophages do not express pro-IL1B until stimulated, typically by TLRs (Franchi et al. 2009). The resulting pro-IL1B is not converted to IL1B unless a second stimulus activates an inflammasome. This requirement for two distinct stimuli allows tight regulation of IL1B/IL18 production, necessary because excessive IL-1B production is associated with numerous inflammatory diseases such as gout and rheumatoid arthritis (Masters et al. 2009).

There are at least four subtypes of the inflammasome, characterized by the NLRP. In addition the protein AIM2 can form an inflammasome. All activate caspase-1. NLRP1 (NALP1), NLRP3 (Cryopyrin, NALP3), IPAF (CARD12, NLRC4) and AIM2 inflammasomes all have clear physiological roles in vivo. NLRP2, NLRP6, NLRP7, NLRP10 and NLRP12 have been demonstrated to modulate caspase-1 activity in vitro but the significance of this is unclear (Mariathasan and Monack, 2007).

NLRP3 and AIM2 bind the protein 'apoptosis-associated speck-like protein containing a CARD' (ASC, also called PYCARD), via a PYD-PYD domain interaction. This in turn recruits procaspase-1 through a CARD-CARD interaction. NLRP1 and IPAF contain CARD domains and can bind procaspase-1 directly, though both are stimulated by ASC. Oligomerization of NLRPs is believed to bring procaspases into close proximity, leading to 'induced proximity' auto-activation (Boatright et al. 2003). This leads to formation of the active caspase tetramer. NLRPs are generally considered to be cytoplasmic proteins, but there is evidence for cytoplasmic-nuclear shuttling of the family member CIITA (LeibundGut-Landmann et al. 2004) and tissue/cell dependent NALP1 expression in the nucleus of neurons and lymphocytes (Kummer et al. 2007); the significance of this remains unclear.

## Literature references

Dixit, VM., Lamkanfi, M. (2009). Inflammasomes: guardians of cytosolic sanctity. *Immunol Rev, 227*, 95-105. ↗

Schroder, K., Tschopp, J. (2010). The inflammasomes. *Cell, 140*, 821-32. ↗

## Editions

| | | |
|---|---|---|
| 2010-04-22 | Authored | Jupe, S. |
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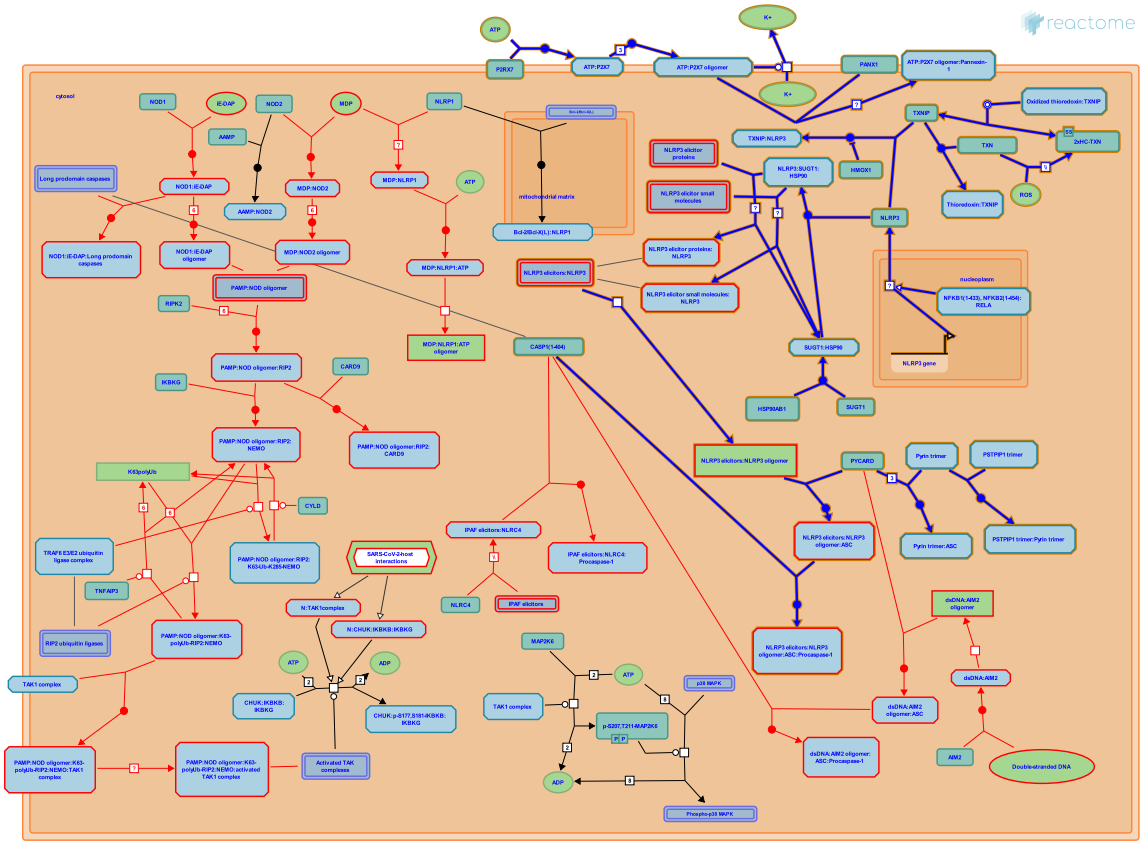
| 2011-06-06 | Reviewed | Rittinger, K., Wong, E. |

## The NLRP3 inflammasome ↗

**Location:** Inflammasomes

**Stable identifier:** R-HSA-844456

**Compartments:** cytosol




The NLRP3 (Cryopyrin) inflammasome is currently the best characterized. It consists of NLRP3, ASC (PYCARD) and procaspase-1; CARD8 (Cardinal) is also suggested to be a component. It is activated by a number of pathogens and bacterial toxins as well as diverse PAMPs, danger-associated molecular patterns (DAMPS) such as hyaluronan and uric acid, and exogenous irritants such as silica and asbestos (see Table S1 Schroder & Tschopp, 2010).
Mutations in NLRP3 which lead to constitutive activation are linked to the human diseases Muckle-Wells syndrome, familial cold autoinflammatory syndrome and NOMID (Ting et al. 2006), characterized by skin rashes and other symptoms associated with generalized inflammation. The cause of these symptoms is uncontrolled IL-1 beta production. Multiple studies have shown that activation of the NLRP3 inflammasome by particulate activators (e.g. Hornung et al. 2008) requires phagocytosis, but this is not required for the response to ATP, which is mediated by the P2X7 receptor (Kahlenberg & Dubyak, 2004) and appears to involve the pannexin membrane channel (Pellegrin & Suprenenant 2006). Direct binding of activators to NLRP3 has not been demonstrated and the exact process of activation is unclear, though it is speculated to involve changes in conformation that free the NACHT domain for oligomerization (Inohara & Nunez 2001, 2003).

## Literature references


Cassel, SL., Sutterwala, FS., Joly, S. (2009). The NLRP3 inflammasome: a sensor of immune danger signals. *Semin Immunol, 21,* 194-8. ↗

Schroder, K., Tschopp, J. (2010). The inflammasomes. *Cell, 140,* 821-32. ↗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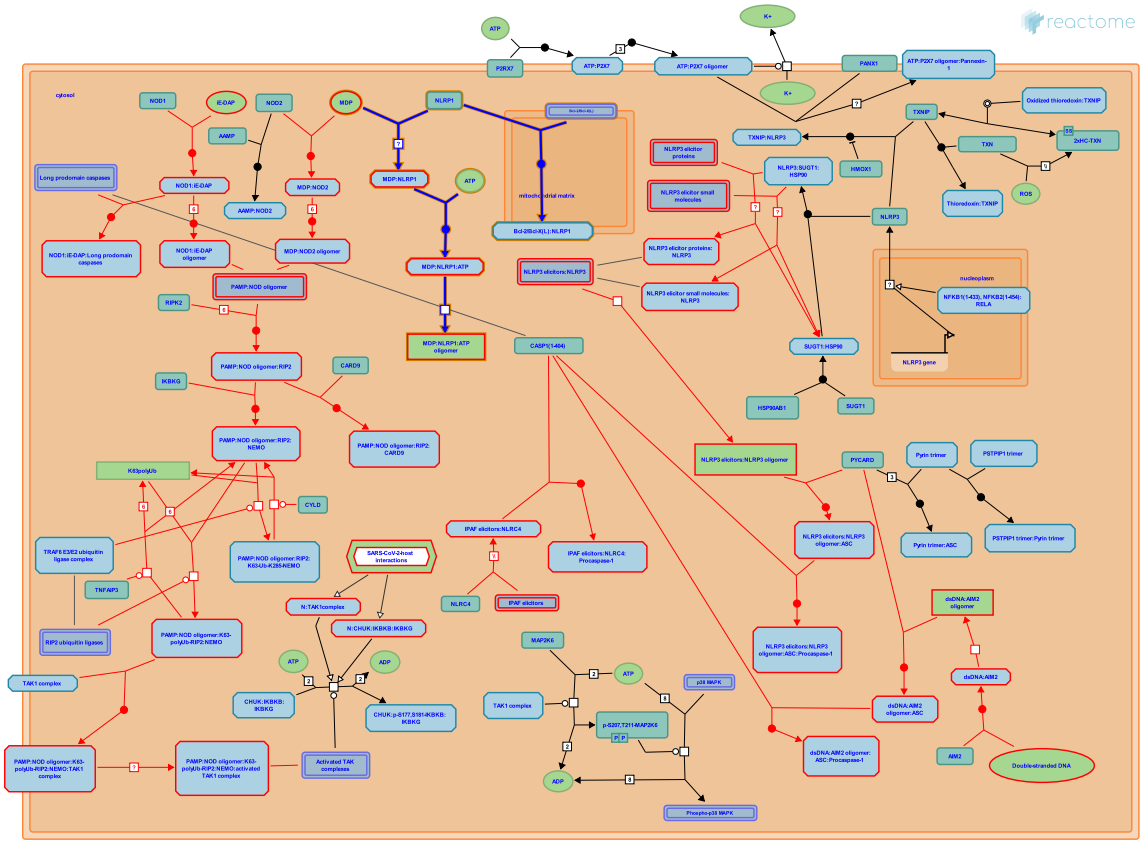
## The NLRP1 inflammasome ↗

**Location:** Inflammasomes

**Stable identifier:** R-HSA-844455

**Compartments:** cytosol



NLRP1 is activated by MDP (Faustin et al. 2007). The NLRP1 inflammasome was the first to be characterized. It was described as a complex containing NALP1, ASC, caspase-1 and caspase-5 (Martinon et al. 2002). Unlike NLRP3, NLRP1 has a C-terminal extension containing a CARD domain, which has been reported to interact directly with procaspase-1, obviating a requirement for ASC (Faustin et al. 2007), though ASC was found to augment the interaction. Mouse NLRP1 has no PYD domain and would therefore not be expected to interact directly with procaspase-1. Like the NLRP3 inflammasome, K+ efflux appears to be essential for caspase-1 activation (Wickliffe et al. 2008). Ribonucleoside triphosphates (NTPs) are required for NALP1-mediated caspase-1 activation with ATP being the most efficient, Mg2+ was also required (Faustin et al. 2007). The human NLRP1 gene has 3 paralogues in mouse that are highly polymorphic. Differences between mouse strains underlie susceptibility to anthrax lethal toxin (Boyden & Dietrich 2006).

## Literature references


Lartigue, L., Reed, JC., Rouiller, I., Bruey, JM., Faustin, B., Sergienko, E. et al. (2007). Reconstituted NALP1 inflammasome reveals two-step mechanism of caspase-1 activation. *Mol Cell, 25*, 713-24. ↗

Burns, K., Martinon, F., Tschopp, J. (2002). The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell, 10*, 417-26. ↗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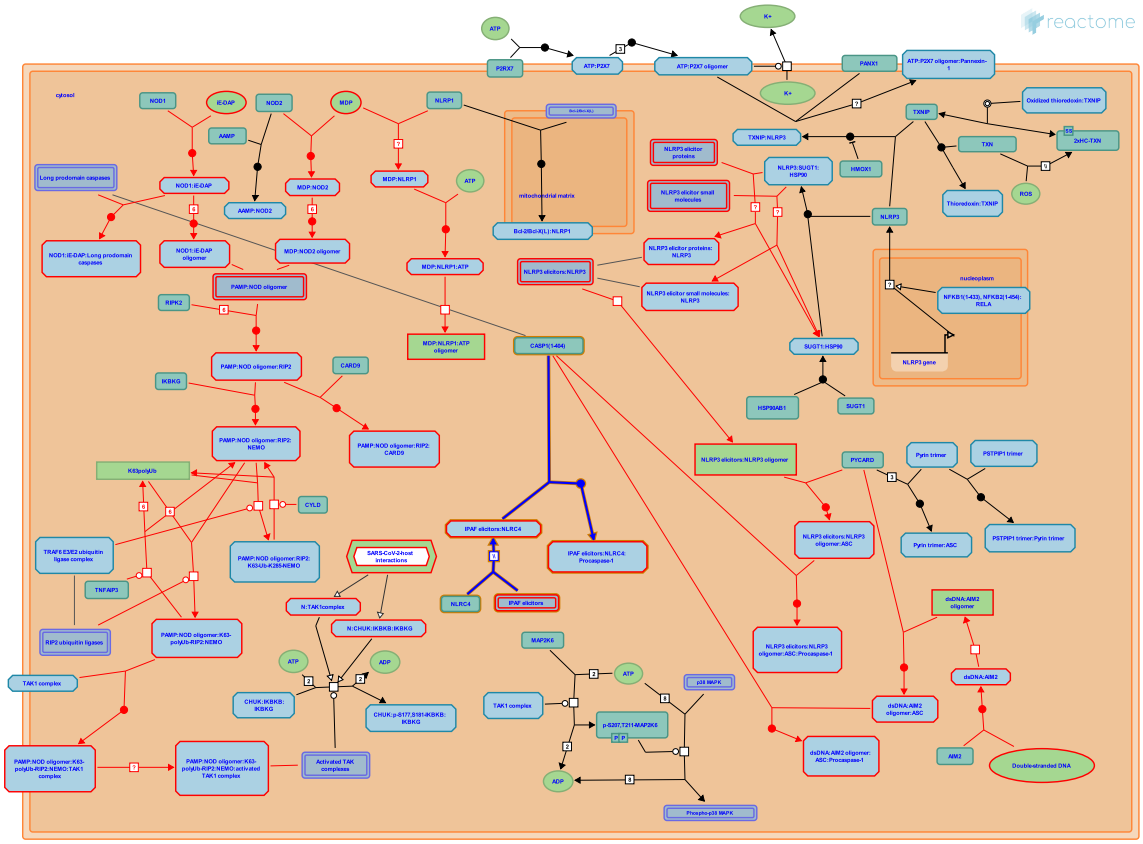
## The IPAF inflammasome ↗

**Location:** Inflammasomes

**Stable identifier:** R-HSA-844623

**Compartments:** cytosol



The IPAF (NLRC4) inflammasome can be activated by several stimuli, most notably by Gram-negative bacteria with either type III or type IV secretion systems that result in cytosolic flagellin, which is recognized by the IPAF inflammasome (Miao et al. 2006). IPAF also recognizes the rod-component of the type III secretion system which shares a sequence motif with flagellin that is essential for detection (Miao et al. 2010). Detection of Legionella and/or flagellin may also involve NAIP5 (Zamboni et al. 2006, Lightfield et al. 2008). IPAF contains a CARD domain and can interact directly with procaspase-1 (Poyet et al. 2001) but ASC increases the maximal activation of caspase-1 in response to S. typhimurium (Mariathasan et al. 2004), S. flexneri, and P. aeruginosa suggesting a possible collaboration with a PYD-containing NLRP for responses to these pathogens (Schroder & Tschopp, 2010). IPAF mediated caspase-1 activation can lead to a particular type of cell death called 'pyroptosis' (see Schroder & Tschopp 2010).

## Literature references


Schroder, K., Tschopp, J. (2010). The inflammasomes. *Cell, 140*, 821-32. ↗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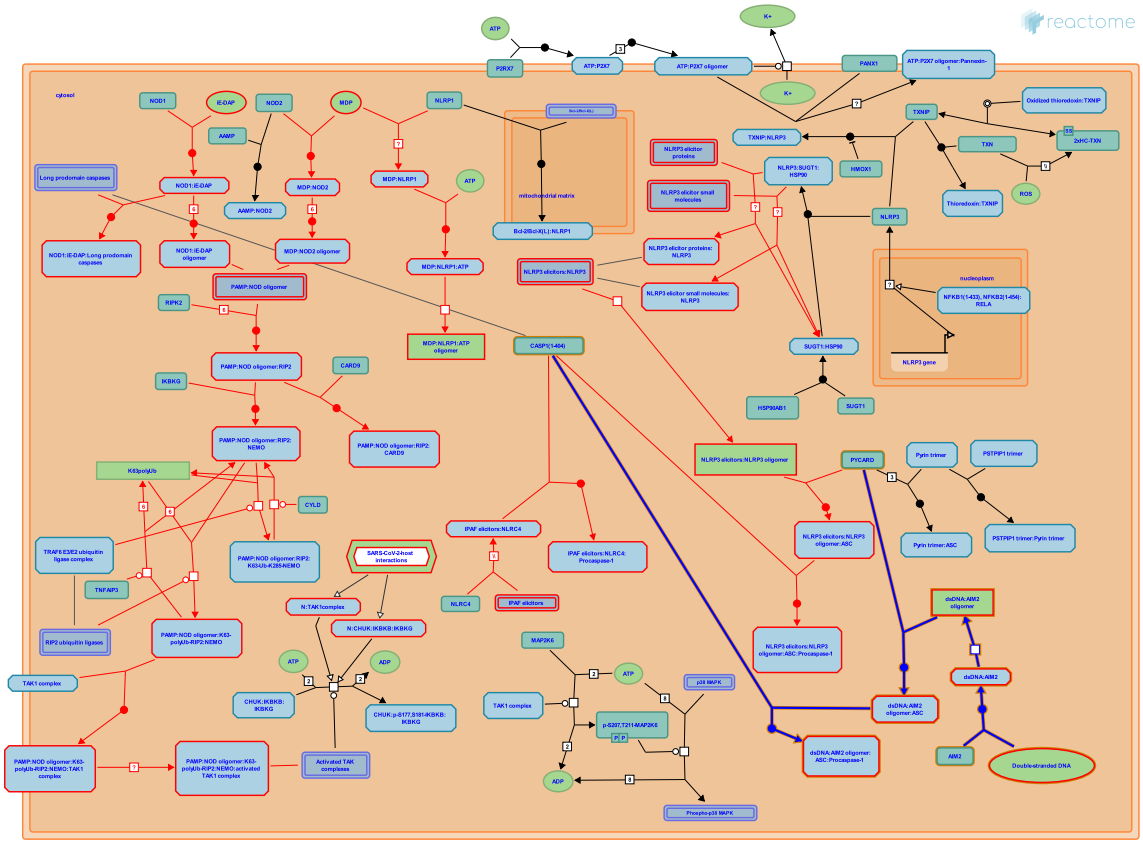
## The AIM2 inflammasome ↗

**Location:** Inflammasomes

**Stable identifier:** R-HSA-844615

**Compartments:** cytosol



AIM2 is a member of the PYHIN or HIN200 family. It has a C-terminal HIN domain which can bind double-stranded DNA (dsDNA) and a PYD domain that can bind ASC via a PYD-PYD interaction. In cells expressing procaspase-1, The interaction of AIM2 with ASC leads to recruitment of procaspase-1 forming the ASC pyroptosome which induces pyroptotic cell death by generating active caspase-1. Data from AIM2 deficient mice indicates that the AIM2 inflammasome is a nonredundant sensor for dsDNA that regulates the caspase-1-dependent maturation of IL-1beta and IL-18 (Rathinam et al. 2010, Hornung & Latz, 2009).

## Literature references


Schroder, K., Tschopp, J. (2010). The inflammasomes. *Cell, 140*, 821-32. ↗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