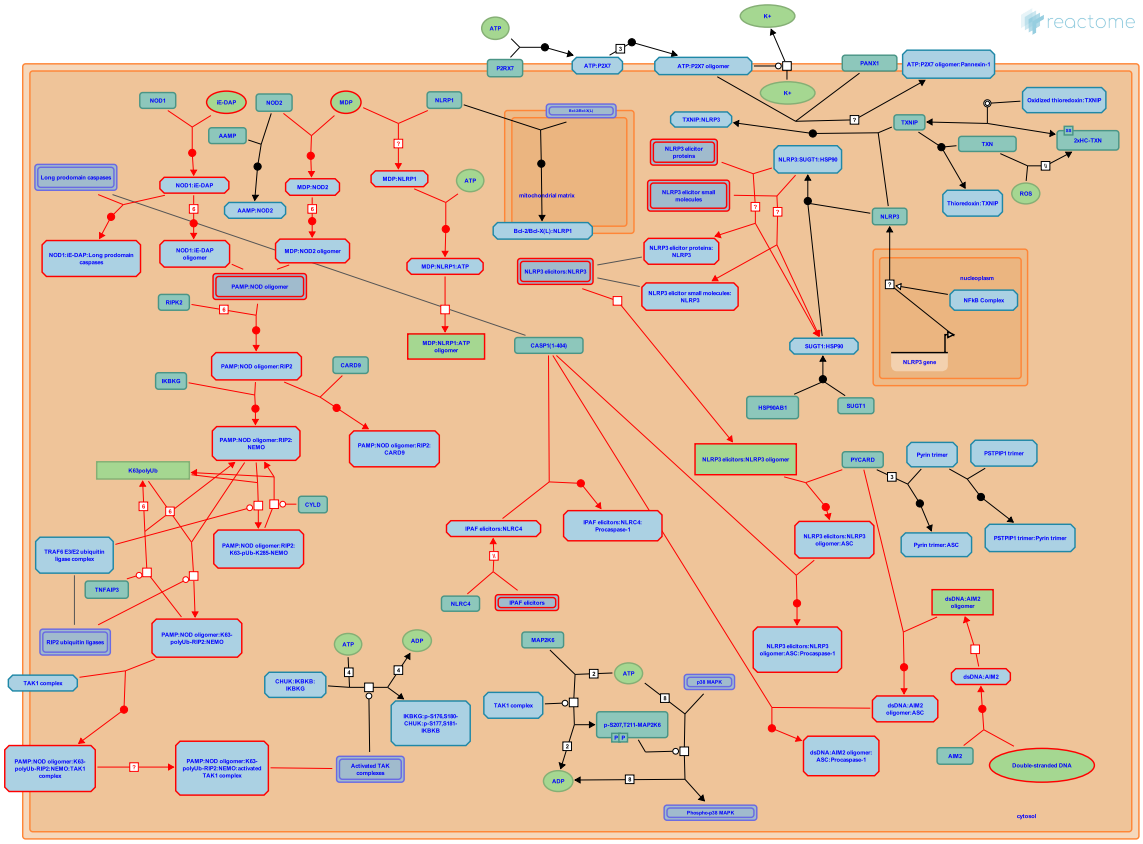
Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways



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29/11/2020

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. ↗

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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: 74

This document contains 3 pathways (see Table of Contents)

Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways ↗

Stable identifier: R-HSA-168643

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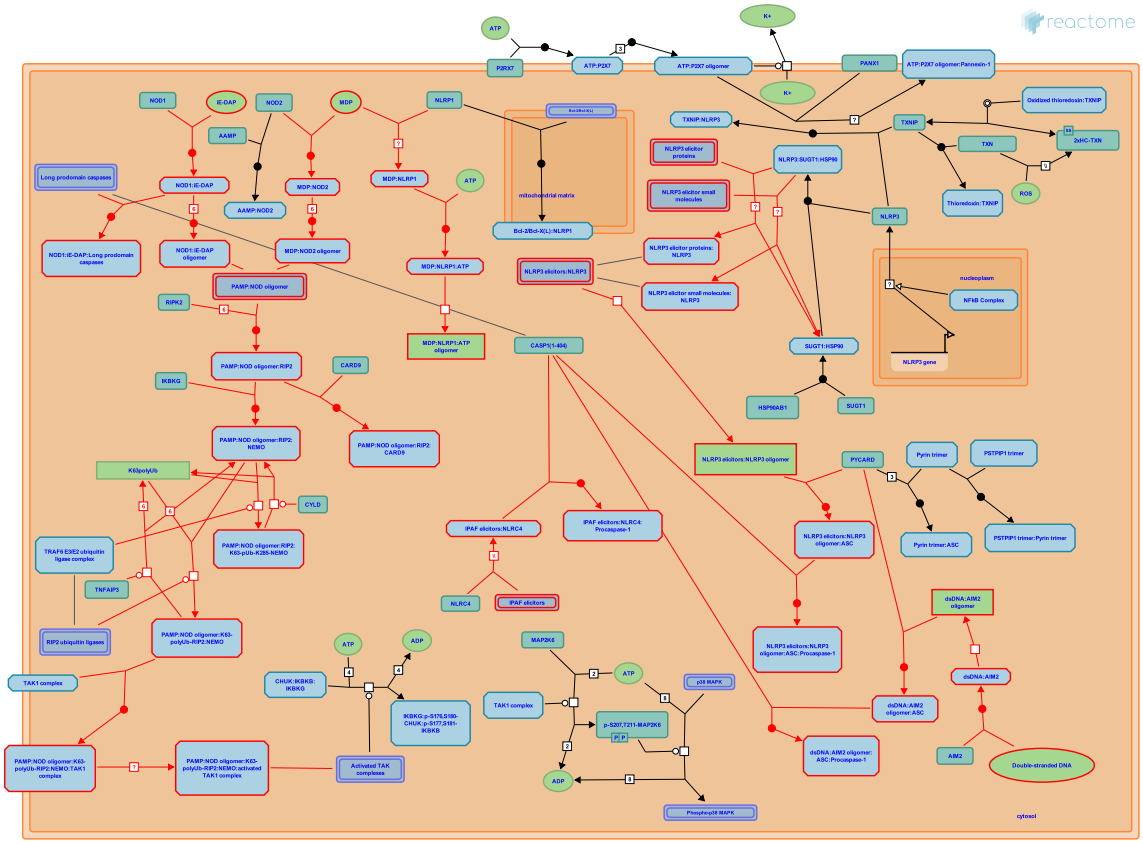


The innate immune system is the first line of defense against invading microorganisms, a broad specificity response characterized by the recruitment and activation of phagocytes and the release of antibacterial peptides. The receptors involved recognize conserved molecules present in microbes called pathogen-associated molecular patterns (PAMPs), and/or molecules that are produced as a result of tissue injury, the damage associated molecular pattern molecules (DAMPs). PAMPs are essential to the pathogen and therefore unlikely to vary. Examples are lipopolysaccharide (LPS), peptidoglycans (PGNs) and viral RNA. DAMPs include intracellular proteins, such as heat-shock proteins and extracellular matrix proteins released by tissue injury, such as hyaluronan fragments. Non-protein DAMPs include ATP, uric acid, heparin sulfate and dsDNA. The receptors for these factors are referred to collectively as pathogen- or pattern-recognition receptors (PRRs). The best studied of these are the membrane-associated Toll-like receptor family. Less well studied but more numerous are the intracellular nucleotide-binding domain, leucine rich repeat containing receptors (NLRs) also called nucleotide binding oligomerization domain (NOD)-like receptors, a family with over 20 members in humans and over 30 in mice. These recognise PAMPs/DAMPs from phagocytosed microorganisms or from intracellular infections (Kobayashi et al. 2003, Proell et al. 2008, Wilmanski et al. 2008). Some NLRs are involved in process unrelated to pathogen detection such as tissue homeostasis, apoptosis, graft-versus-host disease and early development (Kufer & Sansonetti 2011).

Structurally NLRs can be subdivided into the caspase-recruitment domain (CARD)-containing NLRCs (NODs) and the pyrin domain (PYD)-containing NLRPs (NALPs), plus outliers including ice protease (caspase-1) activating factor (IPAF) (Martinon & Tschopp, 2005). In practical terms, NLRs can be divided in-

to the relatively well characterized NOD1/2 which signal via RIP2 primarily to NFkappaB, and the remainder, some of which participate in macromolecular structures called Inflammasomes that activate caspases. Mutations in several members of the NLR protein family have been linked to inflammatory diseases, suggesting these molecules play important roles in maintaining host-pathogen interactions and inflammatory responses.

Most NLRs have a tripartite structure consisting of a variable amino-terminal domain, a central nucleotide-binding oligomerization domain (NOD or NACHT) that is believed to mediate the formation of self oligomers, and a carboxy-terminal leucine-rich repeat (LRR) that detects PAMPs/DAMPs. In most cases the amino-terminal domain includes protein-interaction modules, such as CARD or PYD, some harbour baculovirus inhibitor repeat (BIR) or other domains. For most characterised NLRs these domains have been attributed to downstream signaling

Under resting conditions, NLRs are thought to be present in an autorepressed form, with the LRR folded back onto the NACHT domain preventing oligomerization. Accessory proteins may help maintain the inactive state. PAMP/DAMP exposure is thought to triggers conformational changes that expose the NACHT domain enabling oligomerization and recruitment of effectors, though it should be noted that due to the lack of availability of structural data, the mechanistic details of NLR activation remain largely elusive.

New terminology for NOD-like receptors was adopted by the Human Genome Organization (HUGO) in 2008 to standardize the nomenclature of NLRs. The acronym NLR, once standing for NOD-like receptor, now is an abbreviation of 'nucleotide-binding domain, leucine-rich repeat containing' protein. The term NOD-like receptor is officially outdated and replaced by NLRC where the C refers to the CARD domain. However the official gene symbols for NOD1 and NOD2 still contain NOD and this general term is still widely used.

Literature references

Chen, G., Shaw, MH., Kim, YG., Nunez, G. (2009). NOD-like receptors: role in innate immunity and inflammatory disease. *Annu Rev Pathol, 4*, 365-98. ↗

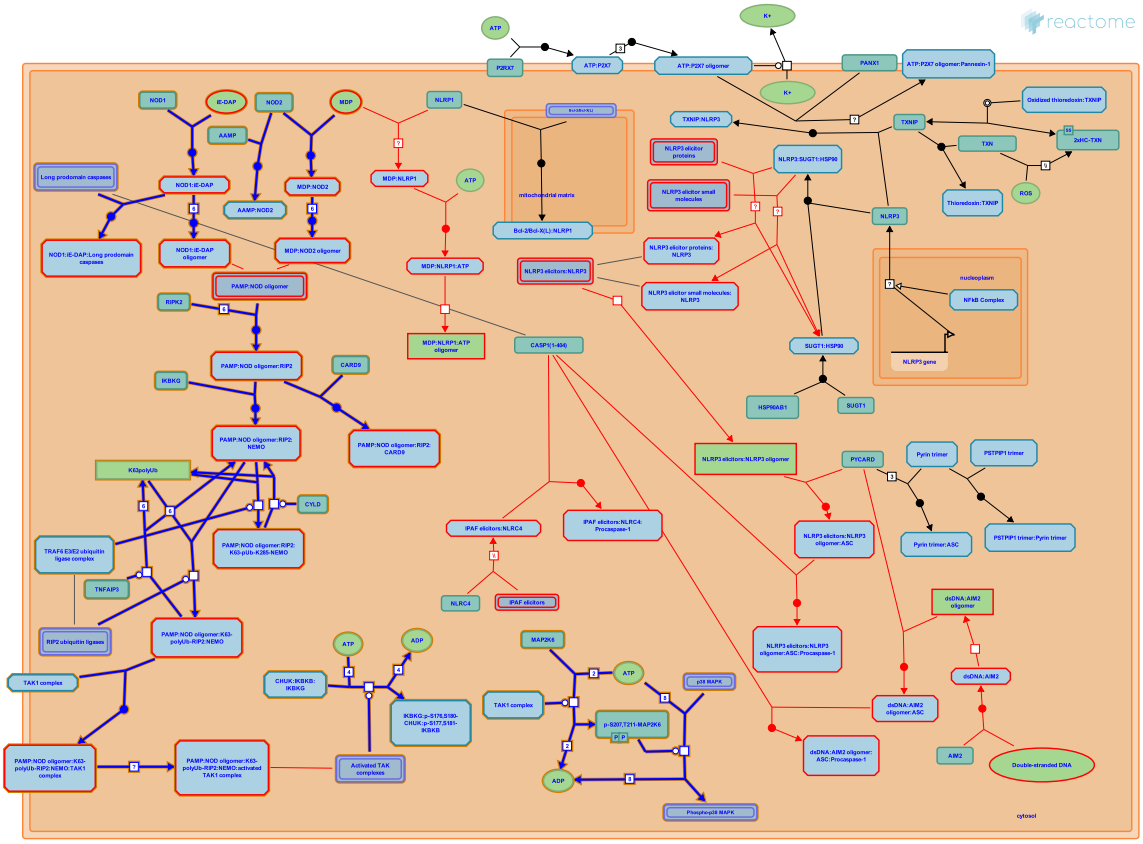
Editions

2010-04-22	Authored	Jupe, S.
2011-04-28	Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.

NOD1/2 Signaling Pathway ↗

Location: Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways

Stable identifier: R-HSA-168638



NOD1 is ubiquitously expressed, while NOD2 expression is restricted to monocytes, macrophages, dendritic cells, and intestinal Paneth cells (Inohara et al. 2005). NOD1 and NOD2 activation induces transcription of immune response genes, predominantly mediated by the proinflammatory transcriptional factor NFkappaB but also by AP-1 and Elk-1 (Inohara et al. 2005). NFkappaB translocates to the nucleus following release from IkappaB proteins. NOD1 and NOD2 signaling involves an interaction between their caspase-recruitment domain (CARD) and the CARD of the kinase RIPK2 (RIP2/RICK). This leads to the activation of the NFkappaB pathway and MAPK pathways (Windheim et al. 2007).

Activated NODs oligomerize via their NACHT domains, inducing physical proximity of RIP2 proteins that is believed to trigger their K63-linked polyubiquitination, facilitating recruitment of the TAK1 complex. RIP2 also recruits NEMO, bringing the TAK1 and IKK complexes into proximity, leading to NF-kappaB activation and activation of MAPK signaling. Recent studies have demonstrated that K63-linked regulatory ubiquitination of RIP2 is essential for the recruitment of TAK1 (Hasegawa et al. 2008, Hitosumatsu et al. 2008). As observed for toll-like receptor (TLR) signaling, ubiquitination can be removed by the deubiquitinating enzyme A20, thereby dampening NOD1/NOD2-induced NF-kappaB activation. NOD1 and NOD2 both induce K63-linked ubiquitination of RIP2, but NOD2-signaling appears to preferentially utilize the E3 ligase TRAF6, while TRAF2 and TRAF5 were shown to be important for NOD1-mediated signaling. In both cases, activation of NF-kappaB results in the upregulated transcription and production of inflammatory mediators.

Literature references

Chen, G., Shaw, MH., Kim, YG., Nunez, G. (2009). NOD-like receptors: role in innate immunity and inflammatory disease. *Annu Rev Pathol, 4*, 365-98. ↗

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Editions

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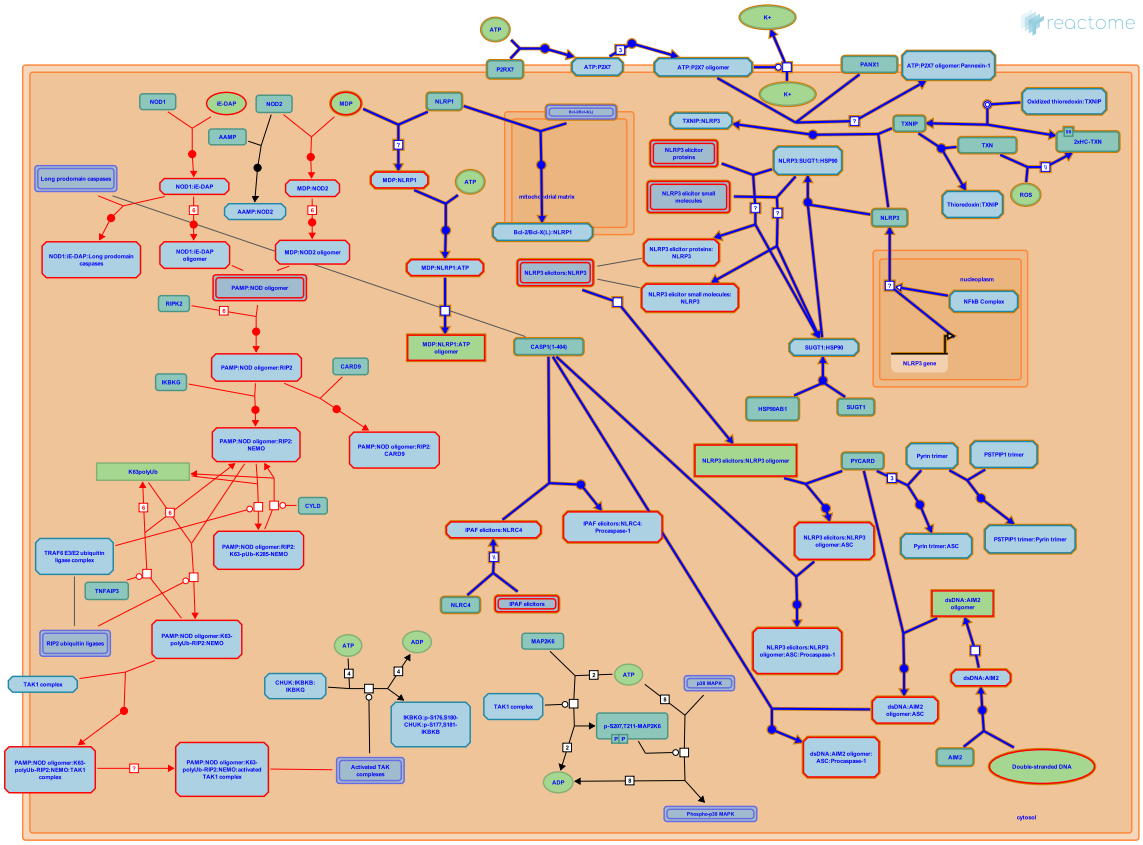
2011-04-28	Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.

Inflammasomes ↗

Location: Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways

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

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

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