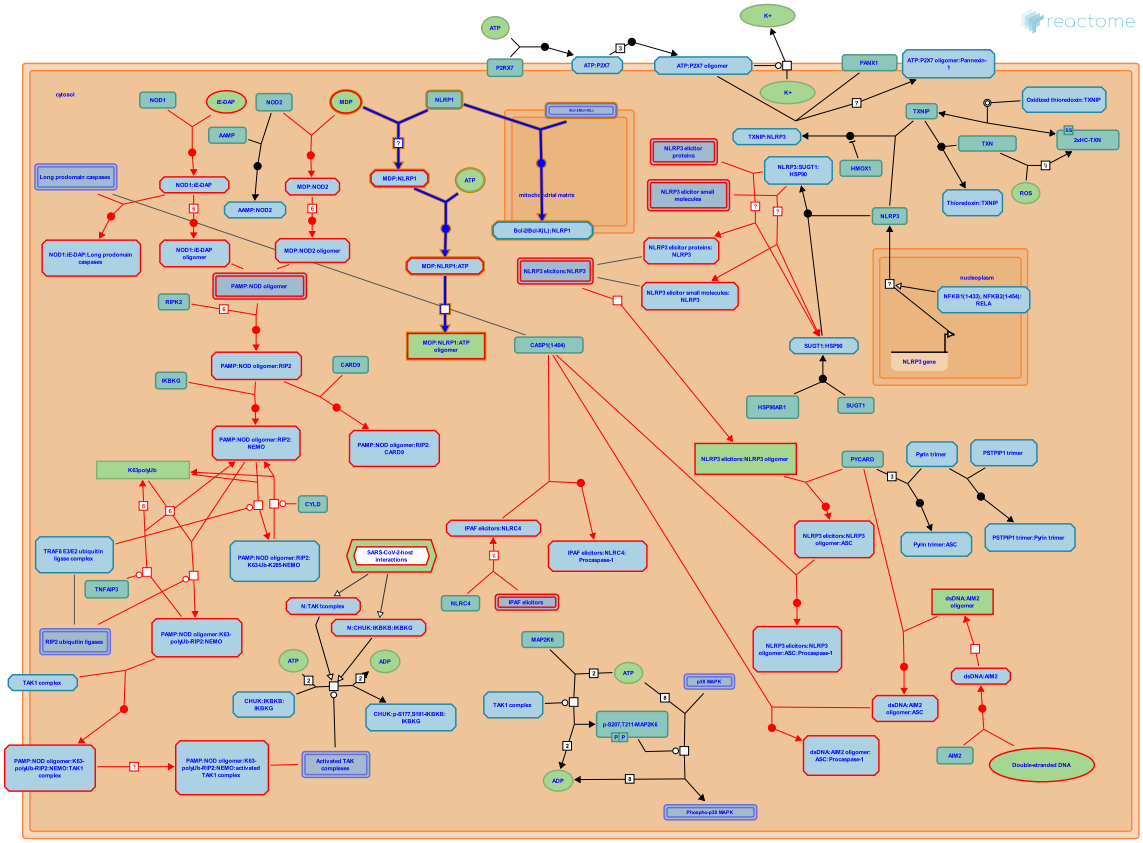
The NLRP1 inflammasome



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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. ↗

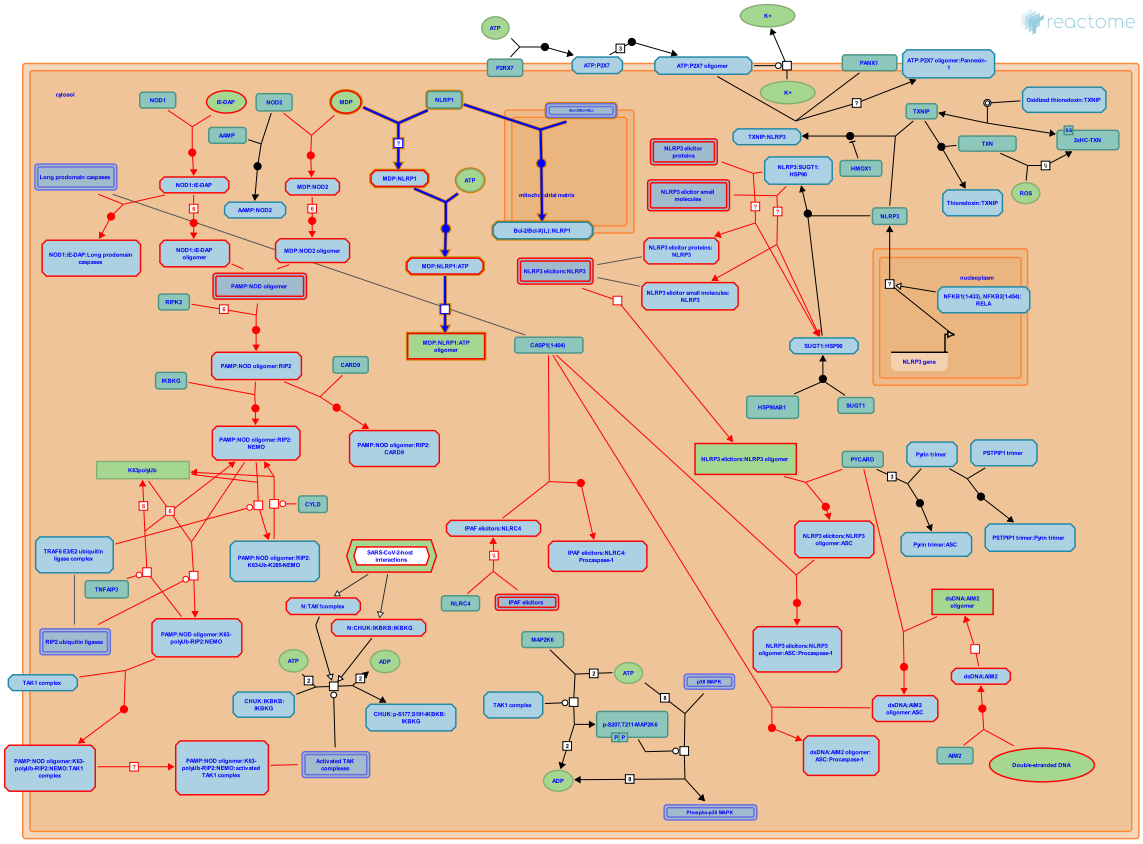
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

The NLRP1 inflammasome ↗

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. ↗

Editions

2010-04-22	Authored	Jupe, S.
2011-04-28	Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.
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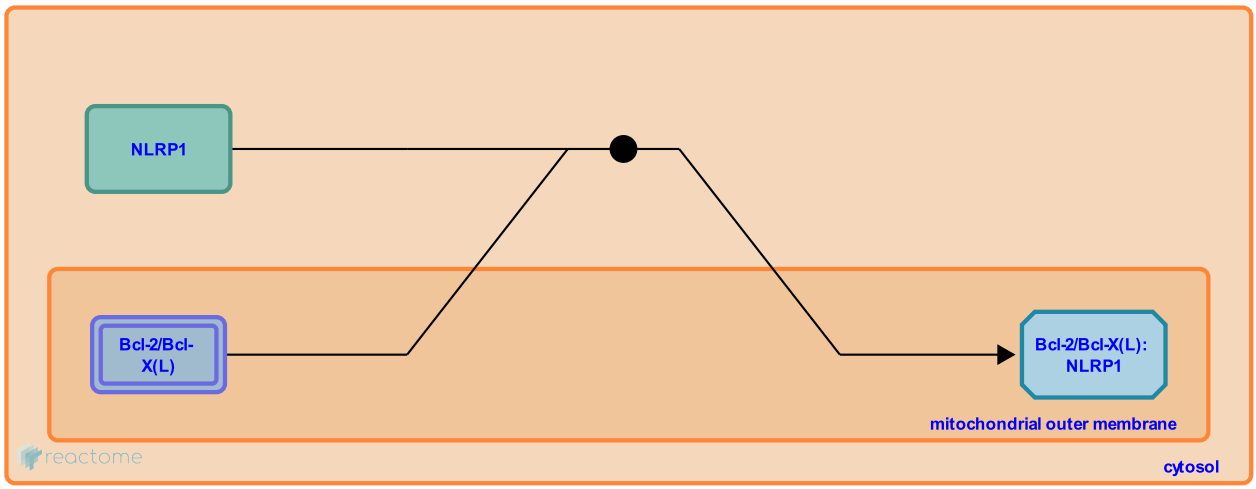
Bcl-2 and Bcl-XL bind NLRP1 ↗

Location: The NLRP1 inflammasome

Stable identifier: R-HSA-879201

Type: binding

Compartments: cytosol, mitochondrial outer membrane



The anti-apoptotic proteins Bcl-2 and Bcl-XL (but not Mcl-1, Bcl-W, Bfl-1 or Bcl-B) bind to NLRP1, preventing MDP-induced activation.

Literature references

Reed, JC., Kress, CL., Xu, C., Balpai, R., Faustin, B., Li, X. et al. (2007). Bcl-2 and Bcl-XL regulate proinflammatory caspase-1 activation by interaction with NALP1. *Cell, 129*, 45-56. ↗

Editions

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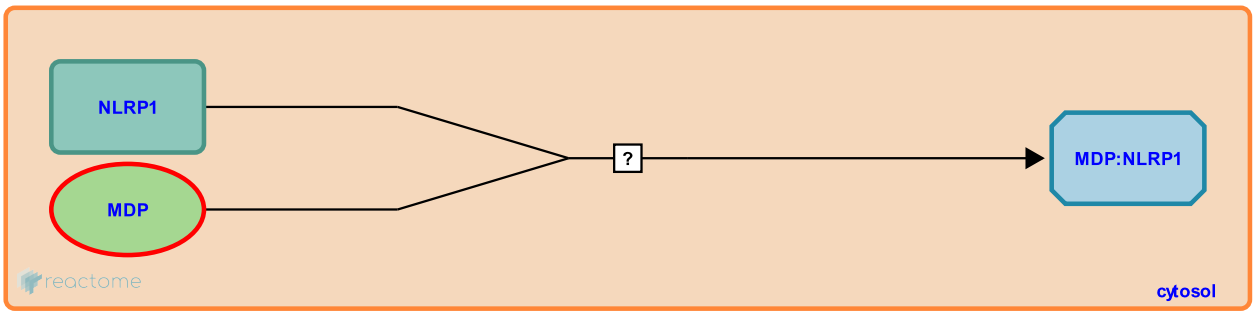
NLRP1 senses MDP ↗

Location: The NLRP1 inflammasome

Stable identifier: R-HSA-844447

Type: uncertain

Compartments: cytosol



In vitro studies using purified NLRP1 and caspase-1 suggest that MDP induces a conformational change in NLRP1 that allows it to bind nucleotides and oligomerize, creating a binding platform for caspase-1 (Faustin et al. 2008). There is no direct evidence that NLRP1 binds MDP so the mechanism that stimulates NLRP1 is unclear.

Followed by: MDP:NLRP1 binds ATP

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. ↗

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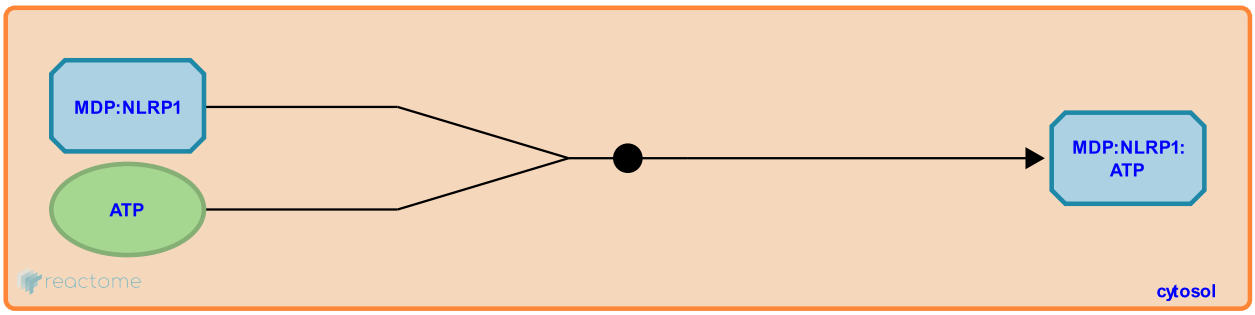
MDP:NLRP1 binds ATP ↗

Location: The NLRP1 inflammasome

Stable identifier: R-HSA-879222

Type: binding

Compartments: cytosol



MDP may induce a conformational change in NLRP1 which enables ATP binding, required for NLRP1 oligomerization (Faustin et al. 2007).

Preceded by: NLRP1 senses MDP

Followed by: NLRP1 oligomerizes

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. ↗

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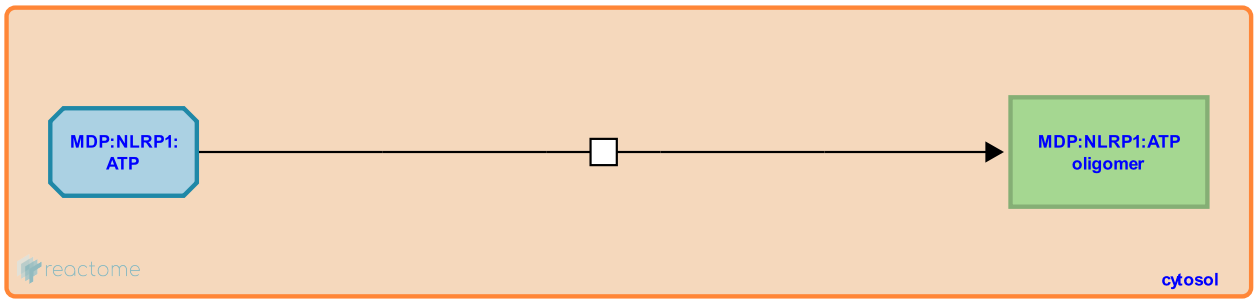
NLRP1 oligomerizes ↗

Location: The NLRP1 inflammasome

Stable identifier: R-HSA-844438

Type: transition

Compartments: cytosol



NLRP1 in the presence of Mg2+ was seen to have altered electrophoretic mobility when MDP was added. This was interpreted as evidence of NLRP1 oligomerization. The extent of oligomerization is unknown.

Preceded by: MDP:NLRP1 binds ATP

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. ↗

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Table of Contents