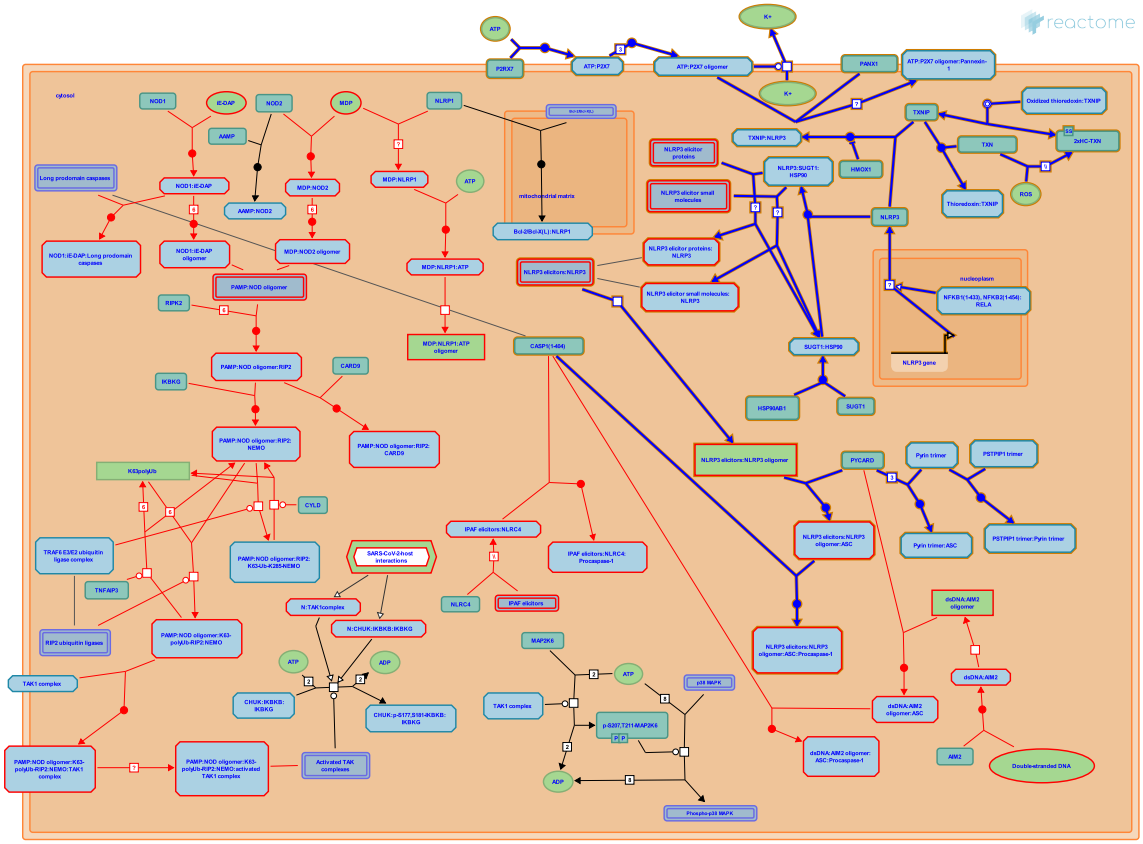
The NLRP3 inflammasome



Jassal, B., Jo, EK., Jupe, S., Kufer, TA., Rittinger, K., Somers, J., Wong, E.

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

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.

08/05/2024

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. ↗

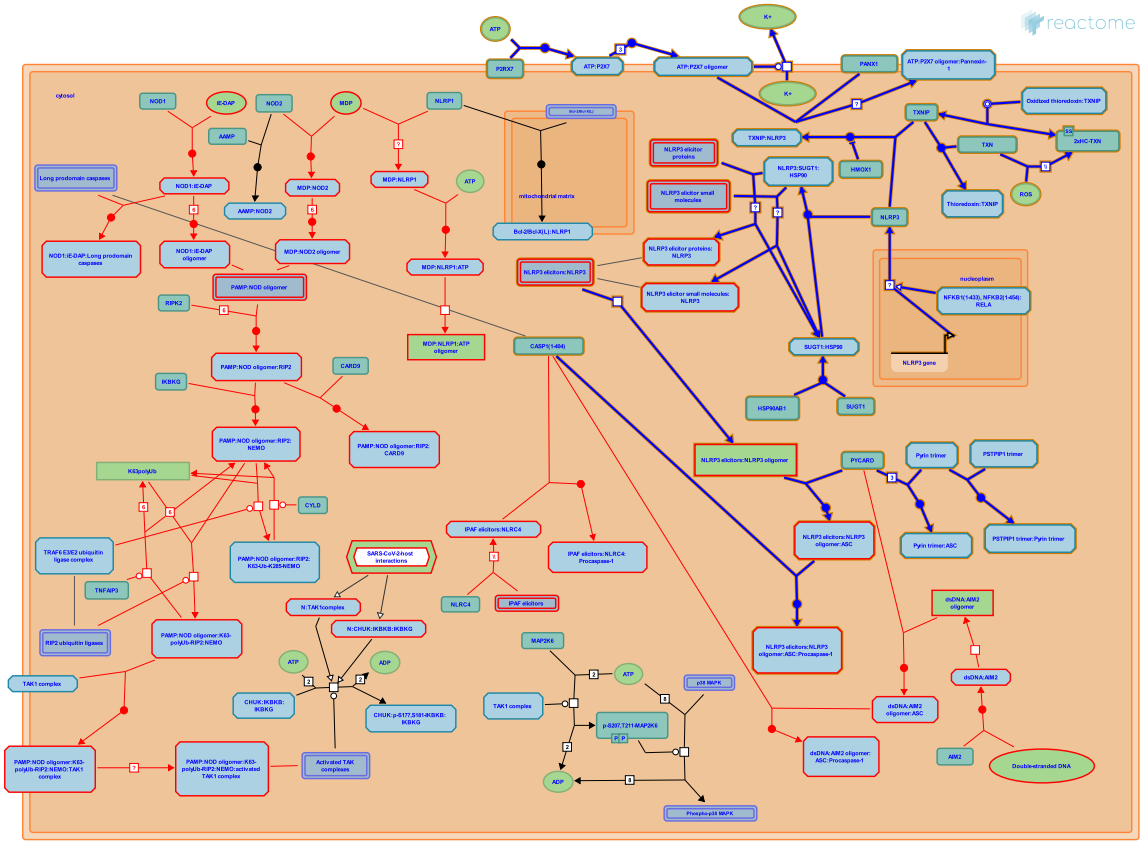
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

The NLRP3 inflammasome ↗

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. ↗

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.

ATP binds to P2X7 ↗

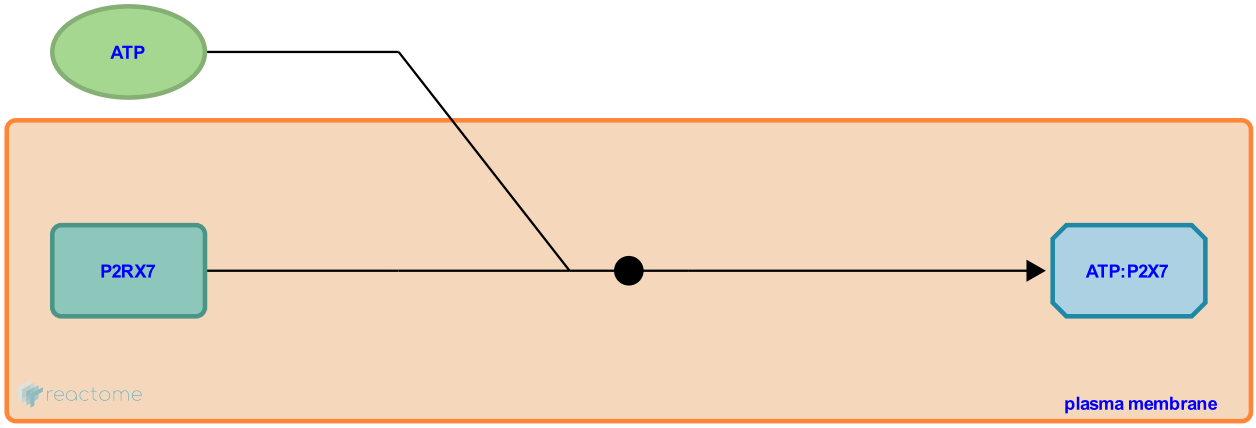
Location: The NLRP3 inflammasome

Stable identifier: R-HSA-877178

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: ATP binds to p2x7 (Rattus norvegicus)



P2X7 is a receptor for extracellular ATP that acts as a ligand gated non-selective cation channel. It is also responsible for the ATP-dependent lysis of macrophages, which it brings about by mediating the formation of membrane pores permeable to large molecules (Adinolfi et al. 2005).

Followed by: P2X7 forms oligomeric non-selective cation channels

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.

P2X7 forms oligomeric non-selective cation channels ↗

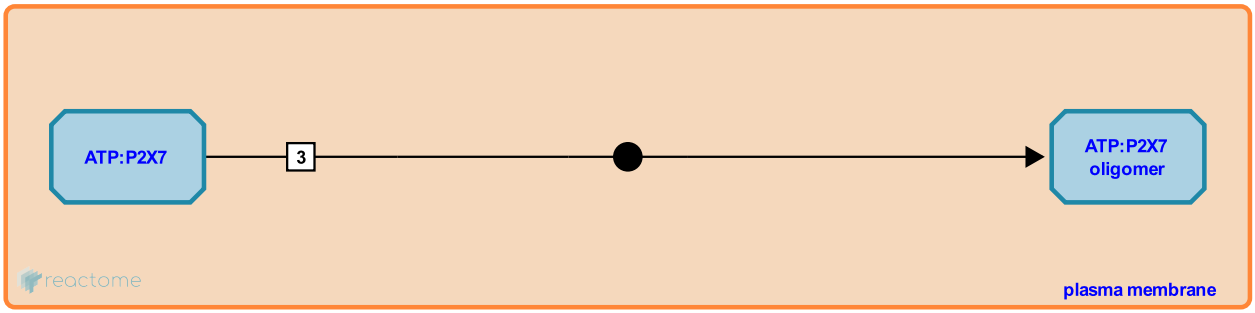
Location: The NLRP3 inflammasome

Stable identifier: R-HSA-877158

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: p2x7 forms oligomeric non-selective cation channels (Rattus norvegicus)



At low to intermediate concentrations of extracellular ATP, P2X4 and P2X7 probably function as heterotrimeric, reversible ATP-gated, non-desensitizing cation channels (Markwardt 2007).

Preceded by: ATP binds to P2X7

Followed by: P2X7 mediates loss of intracellular K+, P2X7 mediates membrane pores that include pannexin-1

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.

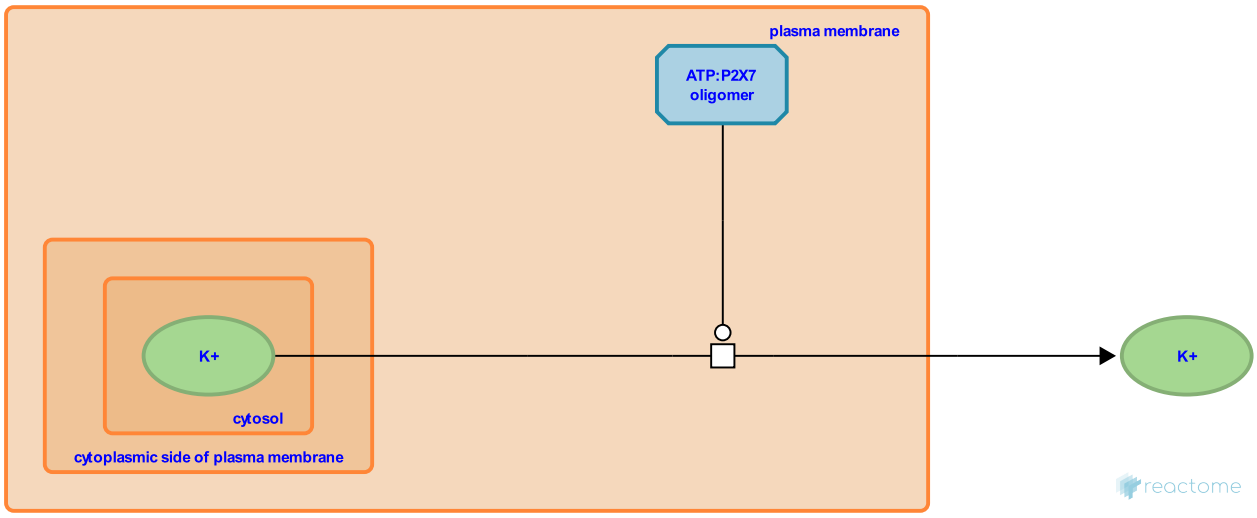
P2X7 mediates loss of intracellular K+

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-877187

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Low level or transient activation of P2X7 leads to reversible opening of a membrane channel permeable to small cations such as Na+, Ca2+ and K+ (Adinolfi et al. 2005).

Preceded by: P2X7 forms oligomeric non-selective cation channels

Followed by: NLRP3 activation by small molecules, NLRP3 activation by elicitor proteins

Literature references

Baricordi, OR., Bolognesi, G., Chiozzi, P., Morelli, A., Falzoni, S., Torboli, M. et al. (2001). Nucleotide receptors: an emerging family of regulatory molecules in blood cells. *Blood, 97*, 587-600.

Klapperstuck, M., Markwardt, F., Bohm, T., Lohn, M. (1997). Purinoceptor-operated cationic channels in human B lymphocytes. *J Physiol, 498*, 143-51.

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.

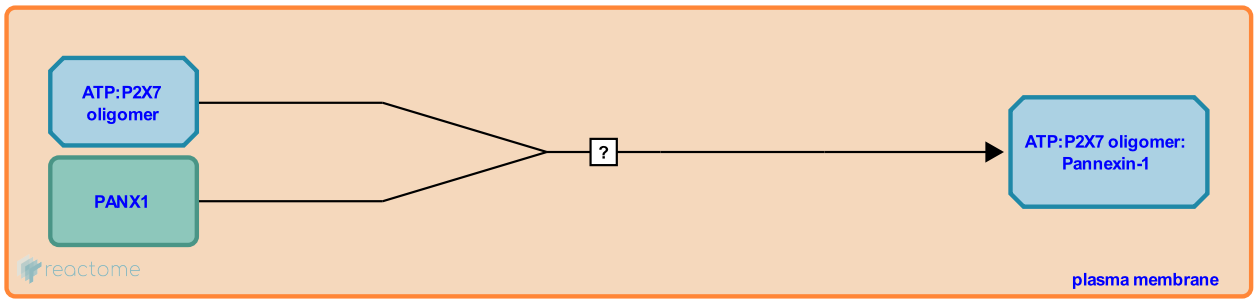
P2X7 mediates membrane pores that include pannexin-1 ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-877198

Type: uncertain

Compartments: plasma membrane



At higher concentrations of extracellular ATP, the P2X7 channel acts as an inducer of nonselective macropores permeable to large (up to 800 Da) inorganic and organic molecules. These 'death complex' pores rapidly leads to complete collapse of ionic gradients, changing the cytosolic environment from high K/ low Na/ low Cl to low K/ high Na/ high Cl (Steinberg et al. 1987, Steinberg & Silverstein 1987, Kahlenberg & Dubyak 2004). The long carboxyl-terminal cytoplasmic domain of P2X7 (352-595) appears to be crucial for P2X7 pore formation (Cheewatrakoolpong et al. 2005, Adinolfi et al. 2005). P2X7 membrane pores were recently shown to include pannexin-1 (Locovei et al. 2007). Pannexins have low homology with the invertebrate innexin gap junction proteins, reported to form gap junction channels and also to function as hemi-gap junction channels that are sensitive to gap junction channel blockers (Bruzzone et al. 2003, 2005). The P2X7 receptor is generally accepted to be part of a multimeric complex, not fully characterized (Kim et al. 2001).

Preceded by: P2X7 forms oligomeric non-selective cation channels

Followed by: NLRP3 activation by small molecules, NLRP3 activation by elicitor proteins

Literature references

Tatham, PE., Lindau, M. (1990). ATP-induced pore formation in the plasma membrane of rat peritoneal mast cells. *J Gen Physiol, 95*, 459-76. ↗

Gomperts, BD., Cockcroft, S. (1979). ATP induces nucleotide permeability in rat mast cells. *Nature, 279*, 541-2. ↗

Surprenant, A., Pelegrin, P. (2006). Pannexin-1 mediates large pore formation and interleukin-1beta release by the ATP-gated P2X7 receptor. *EMBO J, 25*, 5071-82. ↗

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.

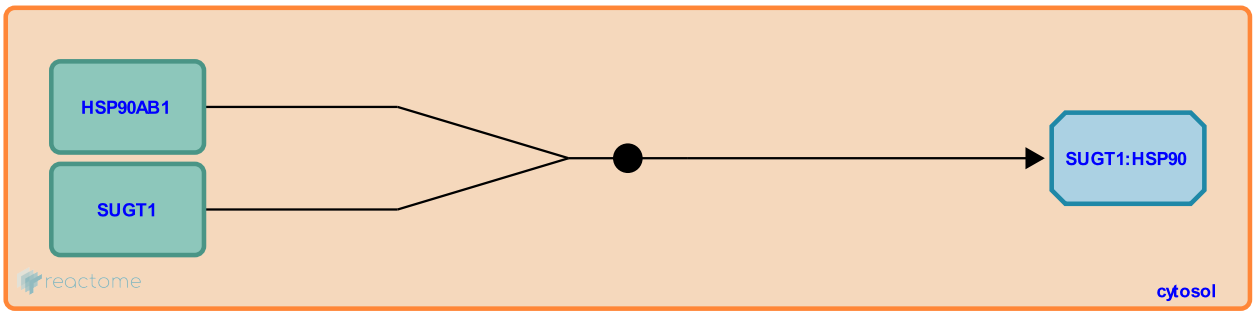
SGT1 binds HSP90

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-874087

Type: binding

Compartments: cytosol



The ubiquitin ligase–associated protein SGT1 (SUGT1) has two putative HSP90 binding domains, a tetratricopeptide repeat and a p23-like CHORD and Sgt1 (CS) domain. The CS domain of human SGT1 physically interacts with HSP90. SGT1 and related proteins are believed to recruit heat shock proteins to multiprotein assemblies (Lee et al. 2004).

Followed by: SGT1:HSP90 binds inactive NLRP3

Literature references

Chazin, WJ., Nowotny, M., Kuznicki, J., Michowski, W., Lee, YT., Jacob, J. (2004). Human Sgt1 binds HSP90 through the CHORD-Sgt1 domain and not the tetratricopeptide repeat domain. *J Biol Chem, 279*, 16511-7.

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.

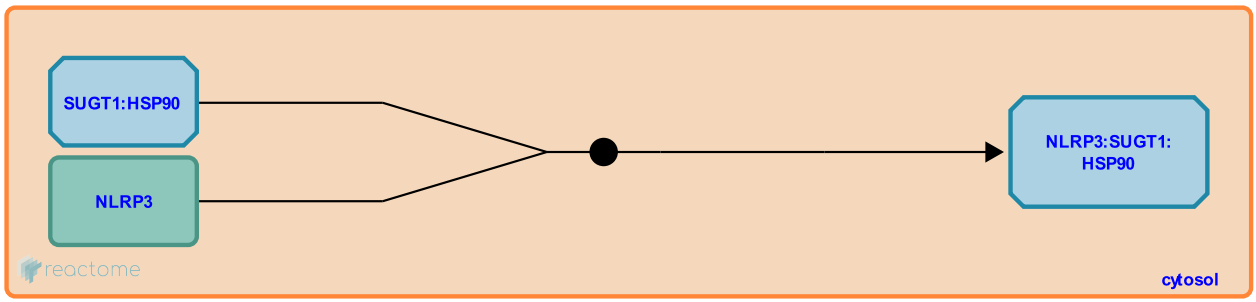
SGT1:HSP90 binds inactive NLRP3 ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-873951

Type: binding

Compartments: cytosol



SGT1 and HSP90 bind the NLRP3 (NALP3) LRR domain. Genetic studies in plants suggest a role for SGT1-HSP90 as co-chaperones of plant resistance (R) proteins, serving to maintain them in an inactive but signaling-competent state. R-protein activation is beleived to lead to dissociation of the SGT1-HSP90 complex. SGT1 and HSP90 are highly conserved, while R proteins are structurally related to mammalian NLRs. Human SGT1 and HSP90 were found to bind NLRP3 (Mayor et al. 2007). Knockdown of human SGT1 by small interfering RNA or chemical inhibition of HSP90 by geldanamycin abrogated NLRP3 inflammasome activity in human monocytic cell line THP-1 (Mayor et al. 2007). Similarly, NLRP3 inflammasome activation was abrogated in geldanamycin-treated human retinal pigment epithelial (RPE) cells (Piippo N et al. 2018). These data indicate that SGT1 and HSP90 are involved in regulation of NLRP3 inflammasome signaling (Mayor et al. 2007; Piippo N et al. 2018).

Preceded by: SGT1 binds HSP90

Followed by: NLRP3 activation by small molecules, NLRP3 activation by elicitor proteins

Literature references

De Smedt, T., Mayor, A., Pétrilli, V., Martinon, F., Tschopp, J. (2007). A crucial function of SGT1 and HSP90 in inflammasome activity links mammalian and plant innate immune responses. *Nat Immunol, 8*, 497-503. ↗

Kinnunen, K., Korhonen, E., Hytti, M., Josifovska, N., Skottman, H., Kaarniranta, K. et al. (2018). Hsp90 inhibition as a means to inhibit activation of the NLRP3 inflammasome. *Sci Rep, 8*, 6720. ↗

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.

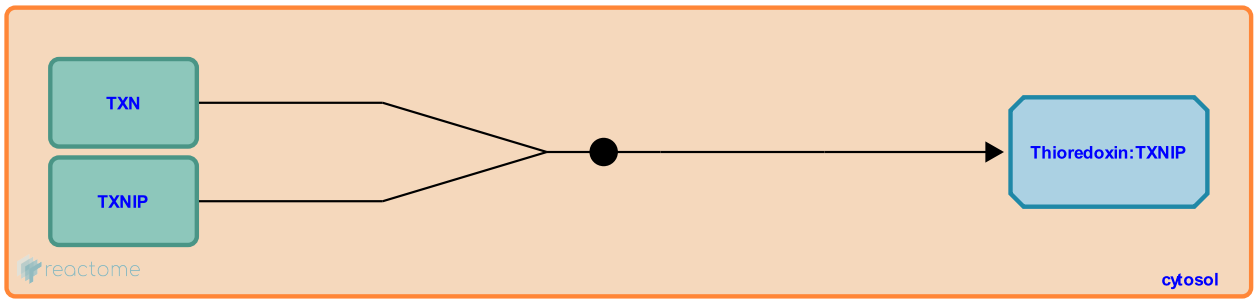
TXNIP binds reduced thioredoxin ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-1250264

Type: binding

Compartments: cytosol



TXNIP interacts with the redox-active domain of thioredoxin (TRX) and is believed to act as an oxidative stress mediator by inhibiting TRX activity or by limiting its bioavailability (Nishiyama et al. 1999, Liyanage et al. 2007).

Preceded by: TXNIP is released from oxidized thioredoxin

Followed by: TXNIP binds NLRP3

Literature references

Liyanage, NP., Lou, MF., Fernando, MR. (2007). Regulation of the bioavailability of thioredoxin in the lens by a specific thioredoxin-binding protein (TBP-2). *Exp Eye Res, 85*, 270-9. ↗

Editions

2011-04-15	Authored	Jupe, S.
2011-04-28	Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.

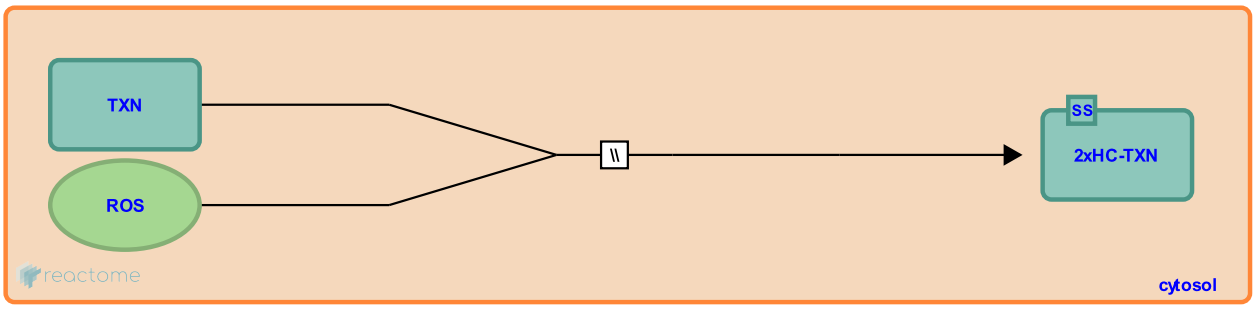
ROS oxidize thioredoxin ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-1250280

Type: omitted

Compartments: cytosol



The presence of reactive oxygen species (ROS) leads to the oxidation of thioredoxin and consequent release of TXNIP (Zhou et al. 2010). The source of the ROS is unclear but they are known to be essential for caspase-1 activation (Cruz et al. 2007) and are produced in response to all known NLRP3 activators (Dostert et al. 2008, Zhou et al. 2010). The freed TXNIP binds NLRP3 and is proposed to activate the NLRP3 inflammasome, explaining how ROS can bring about NLRP3 activation.

Followed by: TXNIP is released from oxidized thioredoxin

Literature references

Choi, I., Thorens, B., Tardivel, A., Zhou, R., Tschopp, J. (2010). Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nat Immunol, 11*, 136-40. ↗

Editions

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

TXNIP is released from oxidized thioredoxin ↗

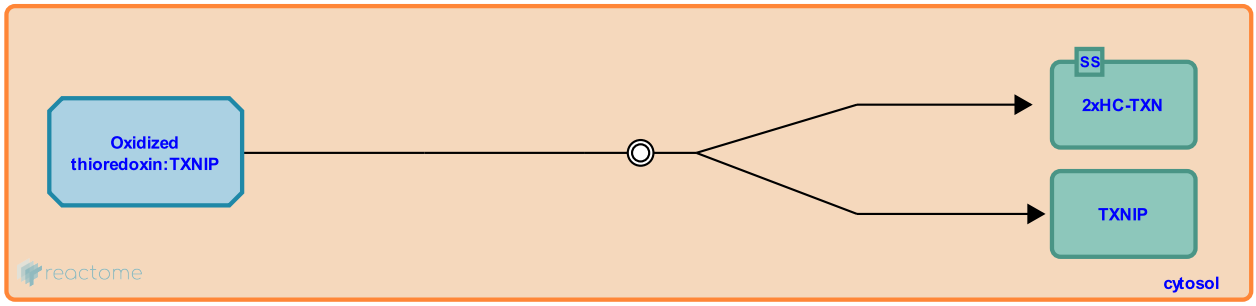
Location: The NLRP3 inflammasome

Stable identifier: R-HSA-1250253

Type: dissociation

Compartments: cytosol

Inferred from: Txnip is released from oxidized thioredoxin (Mus musculus)



ROS induce the dissociation of TXNIP from thioredoxin, freeing TXNIP to subsequently bind NLRP3 and bring about activation of the NLRP3 inflammasome (Zhou et al. 2010).

Preceded by: ROS oxidize thioredoxin

Followed by: TXNIP binds reduced thioredoxin

Editions

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

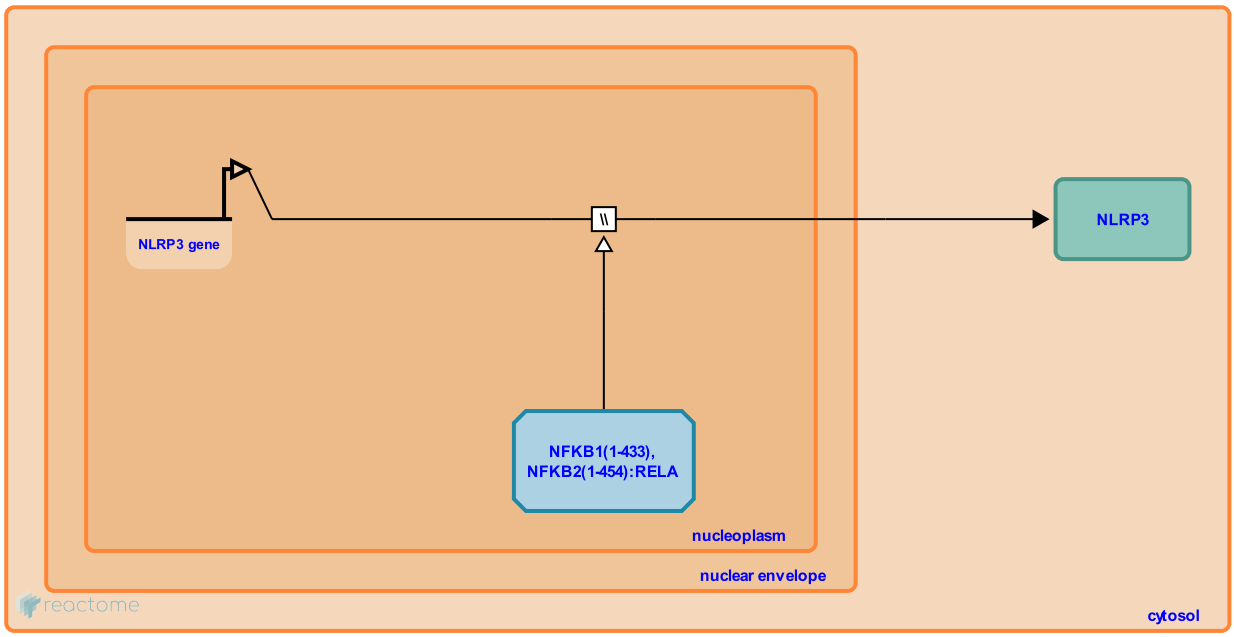
Expression of NLRP3 gene ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-9603905

Type: omitted

Compartments: nucleoplasm, cytosol



Two signals are required for NLRP3 inflammasome activation. Signal 1, also known as the priming signal, is mediated by microbial ligands recognised by TLRs or cytokines such as TNF-α which activate the NF-κB pathway, leading to upregulation of pro-IL-1β and NLRP3 protein levels (Bauernfeind et al. 2009, Jo et al. 2016). In the absence of TLR agonist 'priming', inflammasome dependent caspase-1 activation is observed but IL-1 beta secretion is minimal. This is primarily because pro-IL1 beta is not expressed in most cells until stimulated by proinflammatory signals such as TNF or LPS that activate NFkappaB. NFkappaB induces expression of pro-IL1beta that can be activated by caspase-1.

Followed by: TXNIP binds NLRP3

Literature references

Horvath, G., Fitzgerald, KA., Stutz, A., Wu, J., Bauernfeind, FG., Latz, E. et al. (2009). Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J Immunol, 183,* 787-91. ↗

Jo, EK., Shin, DM., Sasakawa, C., Kim, JK. (2016). Molecular mechanisms regulating NLRP3 inflammasome activation. *Cell. Mol. Immunol., 13,* 148-59. ↗

Editions

2018-03-28	Authored, Edited	Jassal, B.
2018-03-29	Reviewed	Jo, EK.

TXNIP binds NLRP3 ↗

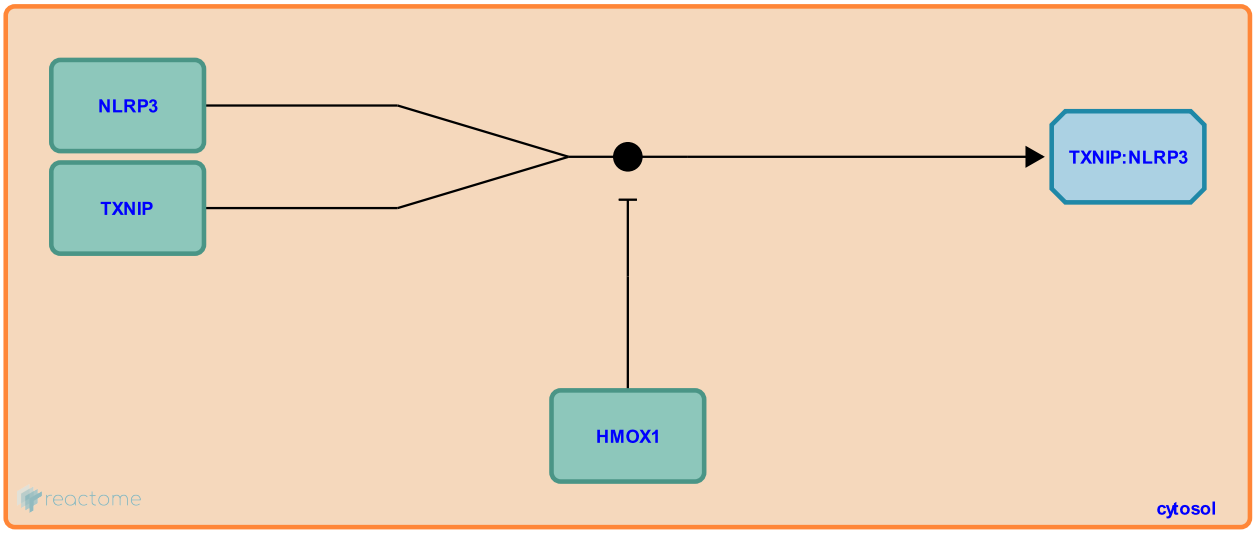
Location: The NLRP3 inflammasome

Stable identifier: R-HSA-1250272

Type: binding

Compartments: cytosol

Inferred from: Txnip binds Nlrp3 (Mus musculus)



Thioredoxin-interacting protein (TXNIP) binds NLRP3. Reactive oxygen species (ROS) such as H2O2 increase this interaction, while the ROS inhibitor APDC blocks it (Zhou et al. 2010). This interaction is proposed to activate the NLRP3 inflammasome.

Heme oxygenase (HMOX1), besides its enzymatic activity of the dimeric membrane protein isoform, also occurs as soluble cytosolic protein. It is probably this form that binds to the NACHT domain of NLRP3, suppressing production of epithelial cell-derived cytokines induced by activation of the NLRP3 inflammasome, and protecting airway epithelium in asthma (Lv et al, 2018).

Preceded by: TXNIP binds reduced thioredoxin, Expression of NLRP3 gene

Followed by: NLRP3 activation by small molecules, NLRP3 activation by elicitor proteins

Literature references

Choi, I., Thorens, B., Tardivel, A., Zhou, R., Tschopp, J. (2010). Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nat Immunol, 11*, 136-40. ↗

Editions

2011-04-28	Authored, Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.
2021-01-23	Reviewed	Somers, J.

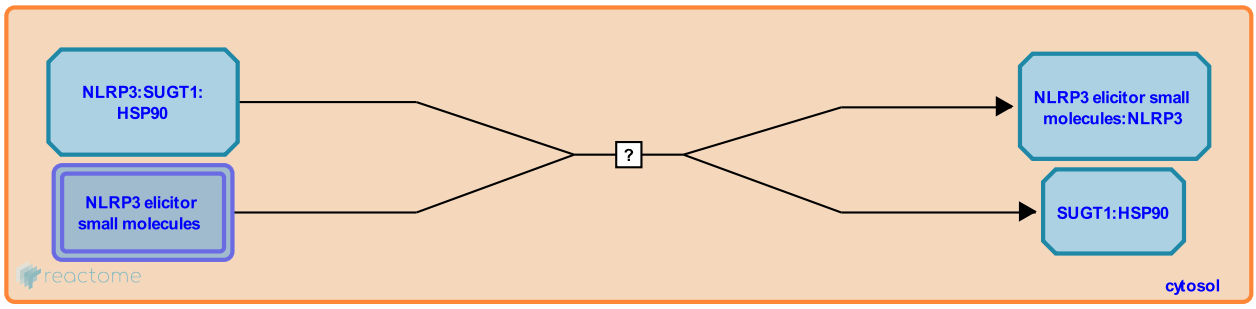
NLRP3 activation by small molecules ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-1306876

Type: uncertain

Compartments: cytosol



The NLRP3 inflammasome is activated by a range of stimuli of microbial, endogenous and exogenous origins including several viruses, bacterial pore forming toxins (e.g. Craven et al. 2009), and various irritants that form crystalline or particulate structures (see Cassel et al. 2009). Multiple studies have shown that phagocytosis of particulate elicitors is necessary for activation (e.g. Hornung et al. 2008) but not 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), which is also involved in the response to nigericin and maitotoxin (Pellegrin & Suprenenant 2007). Direct binding of elicitors to NLRP3 has not been demonstrated and the exact process of activation is unclear, though speculated to involve changes in conformation that make available the NACHT domain for oligomerization (Inohara & Nunez 2001, 2003).

Three overlapping mechanisms are believed to be involved in NLRP3 activation. ATP stimulates the P2X7 ATP-gated ion channel leading to K+ efflux which appears necessary for NLRP3 inflammasome activation (Kahlenberg & Dubyak 2004, Dostert et al. 2008), and is believed to induce formation of pannexin-1 membrane pores. These pores give direct access of NLPR3 agonists to the cytosol. A second mechanism is the endocytosis of crystalline or particulate structures, leading to damaged lysosomes which release their contents (Hornung et al. 2008, Halle et al. 2008). The third element is the generation of reactive oxygen species (ROS) which activate NLRP3, shown to be a critical step for the activation of caspase-1 following ATP stimulation (Cruz et al. 2007). The source of the ROS is unclear.

Preceded by: P2X7 mediates loss of intracellular K+, TXNIP binds NLRP3, P2X7 mediates membrane pores that include pannexin-1, SGT1:HSP90 binds inactive NLRP3

Followed by: NLRP3 oligomerizes via NACHT domains

Literature references

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

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.

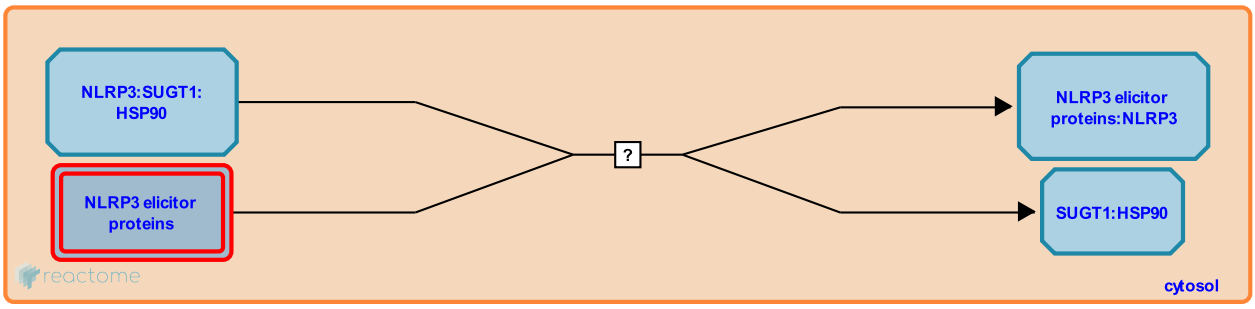
NLRP3 activation by elicitor proteins ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-844440

Type: uncertain

Compartments: cytosol



The NLRP3 inflammasome is activated by a range of stimuli of microbial, endogenous and exogenous origins including several viruses, bacterial pore forming toxins (e.g. Craven et al. 2009), and various irritants that form crystalline or particulate structures (see Cassel et al. 2009). Multiple studies have shown that phagocytosis of particulate elicitors is necessary for activation (e.g. Hornung et al. 2008) but not 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), which is also involved in the response to nigericin and maitotoxin (Pellegrin & Suprenenant 2007). Direct binding of elicitors to NLRP3 has not been demonstrated and the exact process of activation is unclear, though speculated to involve changes in conformation that make available the NACHT domain for oligomerization (Inohara & Nunez 2001, 2003).

Three overlapping mechanisms are believed to be involved in NLRP3 activation. ATP stimulates the P2X7 ATP-gated ion channel leading to K+ efflux which appears necessary for NLRP3 inflammasome activation (Kahlenberg & Dubyak 2004, Dostert et al. 2008), and is believed to induce formation of pannexin-1 membrane pores. These pores give direct access of NLPR3 agonists to the cytosol. A second mechanism is the endocytosis of crystalline or particulate structures, leading to damaged lysosomes which release their contents (Hornung et al. 2008, Halle et al. 2008). The third element is the generation of reactive oxygen species (ROS) which activate NLRP3, shown to be a critical step for the activation of caspase-1 following ATP stimulation (Cruz et al. 2007). The source of the ROS is unclear.

Preceded by: P2X7 mediates loss of intracellular K+, TXNIP binds NLRP3, P2X7 mediates membrane pores that include pannexin-1, SGT1:HSP90 binds inactive NLRP3

Followed by: NLRP3 oligomerizes via NACHT domains

Literature references

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

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.

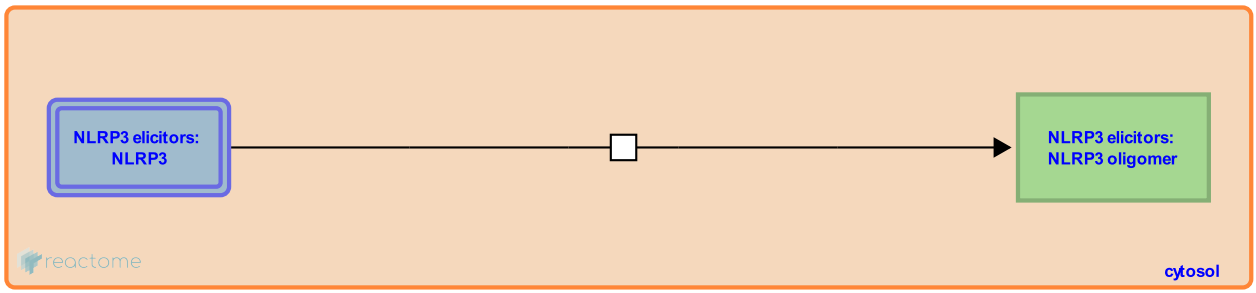
NLRP3 oligomerizes via NACHT domains ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-1296421

Type: transition

Compartments: cytosol



NLRP3 contains a NACHT/NOD domain that in related proteins is responsible for oligomerization (Inohara & Nunez 2001, 2003). NLRP1 forms oligomers upon stimulation with MDP (Faustin et al. 2007) and the enforced oligomerization of NLRP3 PYD domains enhances ASC-dependent effects on apoptosis (Dowds et al. 2002). NOD-mediated oligomerization is widely considered to be part of the activation process for the NLRP3 inflammasome (Schroder et al. 2010, Schroder & Tschopp, 2010). The extent of oligomerization is not known, but models based on the the apoptotic initiator protein Apaf-1 suggest a posible heptameric platform (Proell et al. 2008).

Preceded by: NLRP3 activation by small molecules, NLRP3 activation by elicitor proteins

Followed by: NLRP3 recruits PYCARD (ASC) via a PYD-PYD interaction

Literature references

Mayor, A., Pétrilli, V., Gaide, O., Martinon, F., Tschopp, J. (2007). NALP inflammasomes: a central role in innate immunity. *Semin Immunopathol, 29*, 213-29. ↗

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. ↗

Editions

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

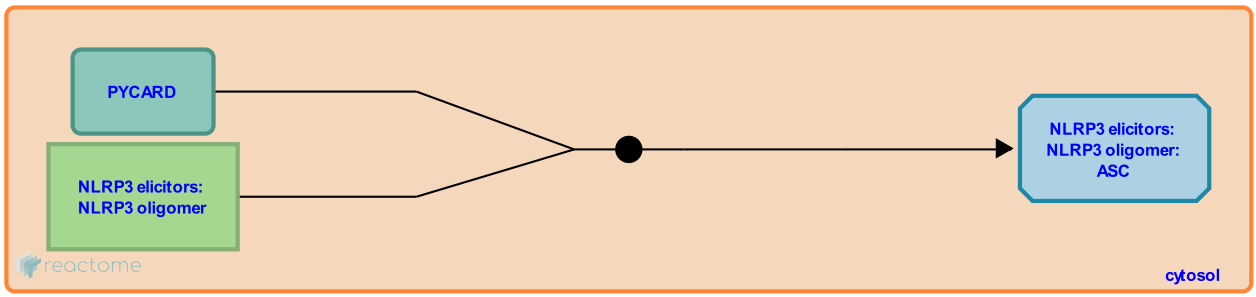
NLRP3 recruits PYCARD (ASC) via a PYD-PYD interaction ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-844610

Type: binding

Compartments: cytosol



NLRP3 interacts with ASC (Manji et al. 2003) via their PYD domains (Dowds et al. 2004). NLRP3 oligomerization leads to PYD domain clustering which is believed to facilitate the interaction of NLRP3 with the PYD domain of ASC (Schroder & Tschopp, 2010).

Preceded by: NLRP3 oligomerizes via NACHT domains

Followed by: Pyrin binds ASC, PYCARD recruits procaspase-1 via CARD

Literature references

Jurman, M., Cao, J., Lora, JM., Bertin, J., Mak, S., Wang, L. et al. (2002). PYPAF1, a PYRIN-containing Apaf1-like protein that assembles with ASC and regulates activation of NF-kappa B. *J Biol Chem, 277*, 11570-5. ↗

Dowds, TA., Masumoto, J., Nunez, G., Inohara, N., Ogura, Y., Chen, FF. (2003). Regulation of cryopyrin/Pypaf1 signaling by pyrin, the familial Mediterranean fever gene product. *Biochem Biophys Res Commun, 302*, 575-80. ↗

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.

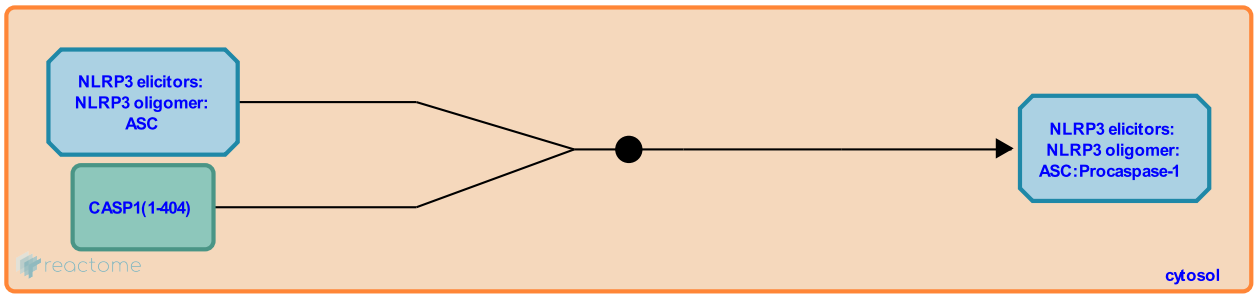
PYCARD recruits procaspase-1 via CARD ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-844612

Type: binding

Compartments: cytosol



Procaspase-1 is recruited via a CARD-CARD interaction with ASC. This creates procaspase-1 clustering which is believed to stimulate procaspase-1 autocleavage, generating the p10/p20 fragments that assemble into the active capsase-1 tetramer (Schroder & Tschopp, 2010).

Preceded by: NLRP3 recruits PYCARD (ASC) via a PYD-PYD interaction

Literature references

Srinivasula, SM., Datta, P., Zhang, Z., Razmara, M., Poyet, JL., Alnemri, ES. (2002). The PYRIN-CARD protein ASC is an activating adaptor for caspase-1. *J Biol Chem, 277*, 21119-22. ↗

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.
2011-06-06	Reviewed	Rittinger, K., Wong, E.

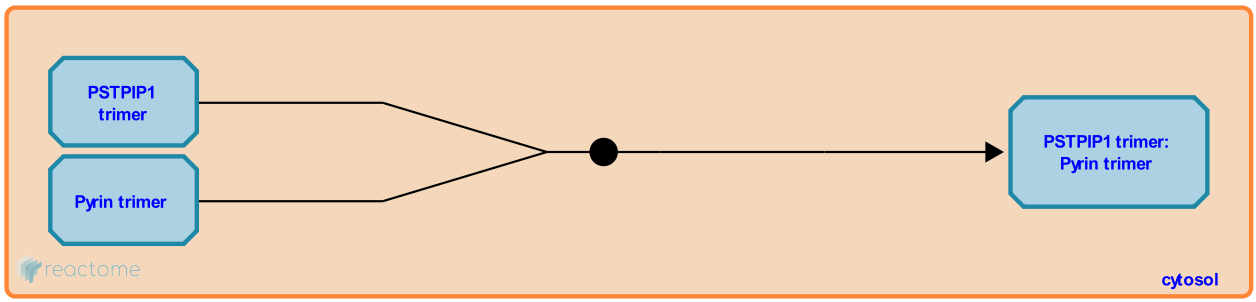
PSTPIP1 binds Pyrin ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-879221

Type: binding

Compartments: cytosol



Proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) is a pyrin-binding protein, involved in regulation of the actin cytoskeleton (Li et al. 1998) and suggested as a regulator of inflammasome activation (Khare et al. 2010). A naturally occurring mutation of PSTPIP1 where Y344 is replaced by F blocks tyrosine phosphorylation and reduces pyrin binding. Mutations of PSTPIP1 that increase pyrin binding are associated with the inflammatory syndrome pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA). Expression of PSTPIP1 with these mutations in THP-11 cells resulted in substantially increased caspase-1 activation and IL-1beta secretion. PSTPIP1 binding to pyrin is believed to promote the unmasking of its PYD domain and enhance interactions with ASC, facilitating ASC oligomerization and caspase-1 recruitment (Yu et al. 2007).

Followed by: Pyrin binds ASC

Literature references

Shoham, NG., Hull, KM., Wood, G., Centola, M., Wise, CA., Mansfield, E. et al. (2003). Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci U S A, 100*, 13501-6. ↗

Editions

2010-04-22	Authored	Jupe, S.
2011-04-28	Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.

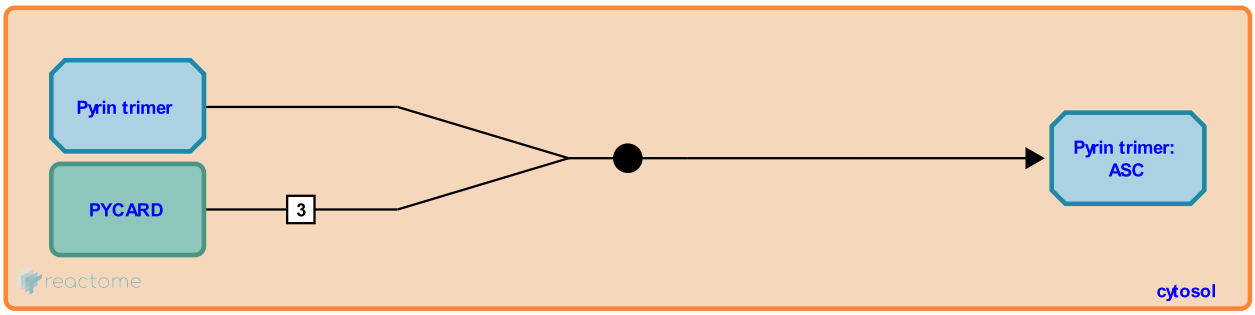
Pyrin binds ASC ↗

Location: The NLRP3 inflammasome

Stable identifier: R-HSA-877361

Type: binding

Compartments: cytosol



Trimeric pyrin interacts with ASC through its Pyrin domains, leading to oligomerization of ASC. This interaction interferes with the ability of NLRP3 (Cyropyrin) to associate with ASC and thus inhibits inflammasome activation (Chae et al. 2003).

Preceded by: NLRP3 recruits PYCARD (ASC) via a PYD-PYD interaction, PSTPIP1 binds Pyrin

Literature references

Schaner, P., Richards, N., Shelden, E., Wadhwa, A., Stuckey, J., Diaz, A. et al. (2001). Interaction between pyrin and the apoptotic speck protein (ASC) modulates ASC-induced apoptosis. *J Biol Chem, 276*, 39320-9. ↗

Dowds, TA., Masumoto, J., Nunez, G., Inohara, N., Ogura, Y., Chen, FF. (2003). Regulation of cryopyrin/Pypaf1 signaling by pyrin, the familial Mediterranean fever gene product. *Biochem Biophys Res Commun, 302*, 575-80. ↗

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.

Table of Contents