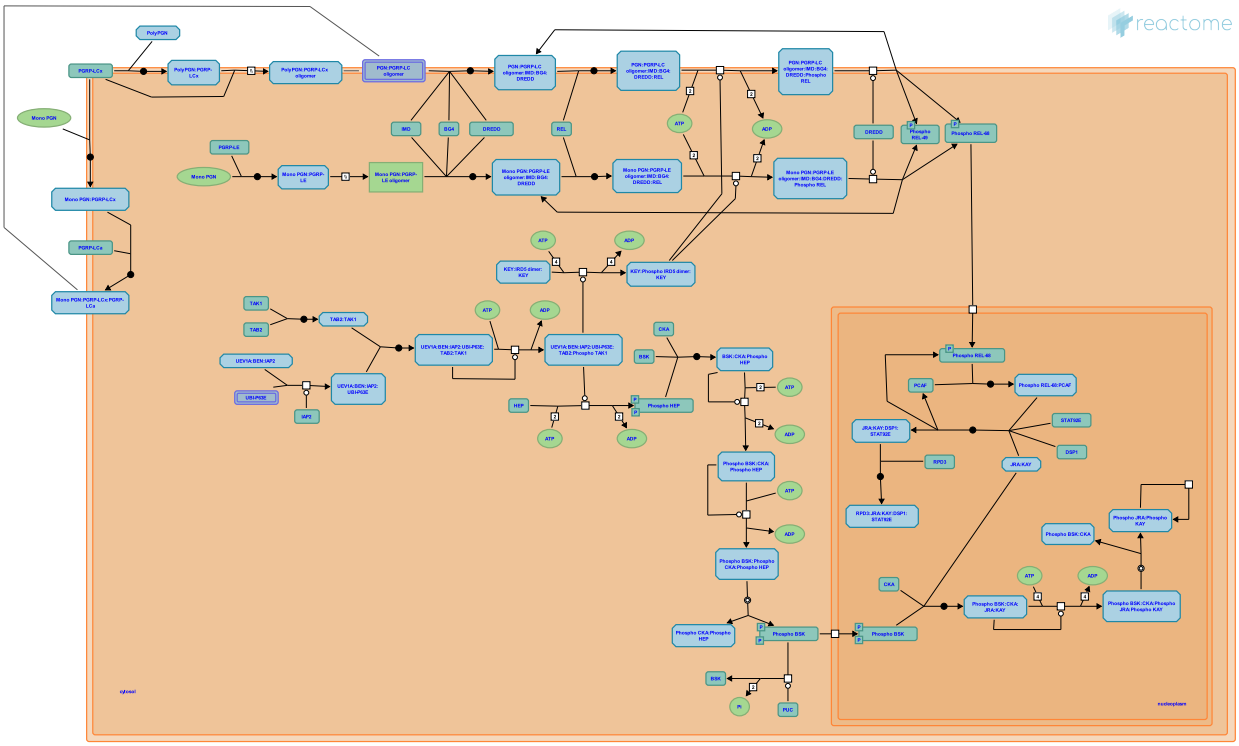
Imd pathway



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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).

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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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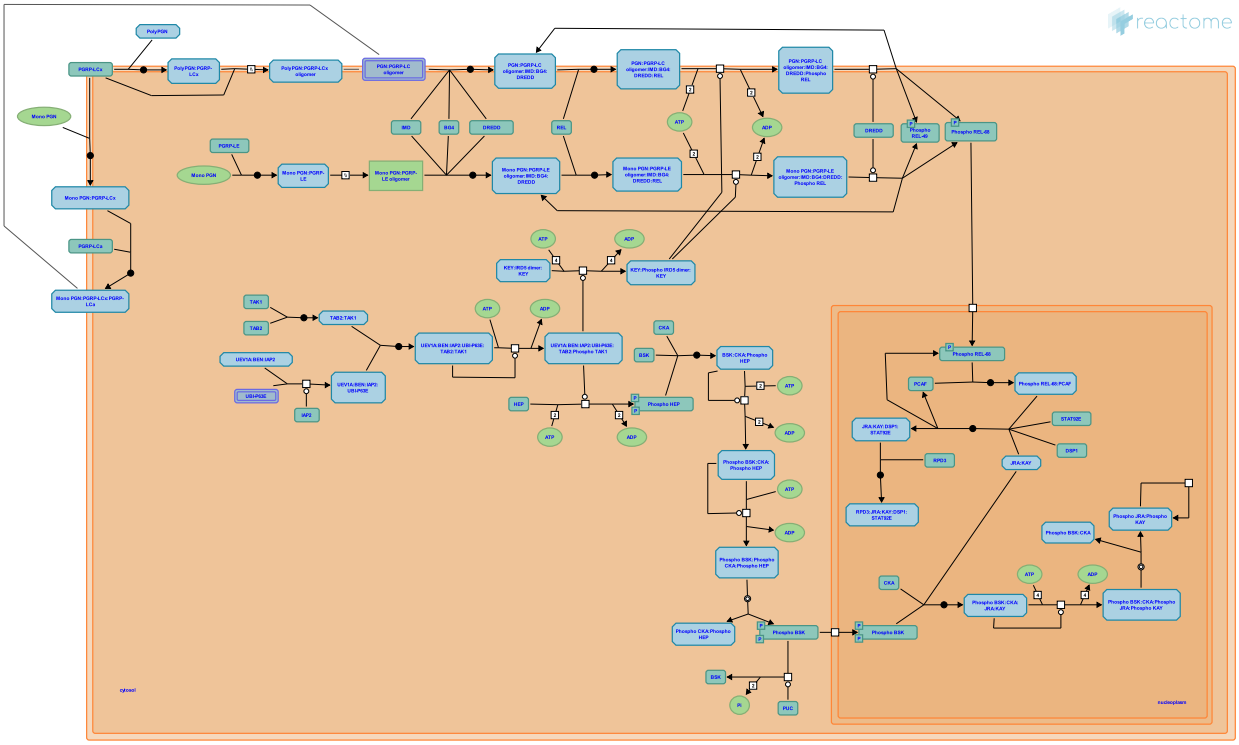
Imd pathway ↗

Stable identifier: R-DME-209459



The Imd pathway mediates the response of Drosophila to the presence of diaminopimelic acid-type peptidoglycan (DAP-PGN) found in all Gram negative and many Gram positive bacteria, over lysine-type PGN found in Gram positive bacteria. It operates in the fat-body and hemocytes in response to a systemic infection and is activated upon recognition of DAP-PGN by the PGRP-LC/LE receptors, which leads to activation of the NFkappaB-like transactivator Relish (REL). Elements regulated by the pathway during a systemic infection have been identified by microarray and include a large set of antibacterial peptides genes (De Gregorio et al., 2002; Boutros et al., 2002). In addition, the Imd pathway plays an important role in the relationship many epithelia have with the external world, where it mediates the local inducible immune response (Tzou et al., 2000; Zaidman-Remy et al., 2006). The canonical component of the Imd pathway contains: PGRP-LC (Gottar et al., 2002; Choe et al., 2002; Ramet et al., 2002), IMD (Georgel et al., 2001), DFADD (BG4) (Leulier et al., 2002; Naitza et al., 2002), DREDD (Leulier et al., 2000), REL (Hedengren et al., 1999), Kenny (KEY) and IRD5 (Silverman et al., 2000; Rutschmann et al., 2000; Lu et al., 2001), TAK1 (Vidal et al., 2001; Silverman et al., 2003), TAB2 (Gesellchen et al., 2005; Kleino et al., 2005; Zhuang et al., 2006), Inhibitor of apoptosis 2 (IAP2) (Gesellchen et al., 2005; Kleino et al., 2005; Leulier et al., 2006). Flies lacking these genes are viable but are highly susceptible to Gram negative bacterial infection (Lemaitre et al., 1995). It is not clear if this pathway plays another role beside immunity but overactivation of the Imd pathway induces strong lethality due to apoptosis (Georgel et al., 2001). It should also be noted that the Imd pathway is present and functional in almost all epithelial cells. However, the responses in these tissues are not identical to those observed in the fat body (or in cell culture). In particular, the outputs of Imd signalling are significantly modified in the gut. During Imd signalling in the gut, gene targets producing PGN-digesting PGRP-LB and -SC proteins are expressed but other REL target genes, especially the AMP genes are mostly silent.

In response to infection by Gram-negative bacteria the Imd pathway of the innate immunity response is activated. DAP-PGNs, found on Gram-negative bacteria, are recognised and bind to the PGRP-LC receptor at the plasma membrane or intracellularly bind to the PGRP-LE receptor. This causes the receptor to dimerise/multimerise and activate resulting in the recruitment of the adaptor proteins IMD and DFADD (BG4) along with the caspase 8 orthologue DREDD. Meanwhile, the Ser/Thr MAPK kinase kinase, TAK1 and its partner TAB2 are activated possibly through the IAP2:Bendless (BEN):UEV1a ubiquitin E3 ligase complex. TAK1 and TAB2, in turn phosphorylate the IKKbeta orthologue IRD5. Activated IRD5, in complex with IKKgamma orthologue Kenny (KEY), phosphorylates the NFkappaB orthologue Relish (REL). REL consists of an N-terminal nuclear factor containing domain (REL-68) and an inhibitory C-terminal domain (REL-49) responsible for anchoring REL in the cytoplasm. REL is then cleaved by the caspase, DREDD, releasing the N-terminal domain REL-68. This translocates to the nucleus where it is able to activate transcription of genes encoding antimicrobial peptides.

In addition to being a key component of the Imd pathway, TAK1 kinase is involved in triggering a JNK kinase signalling cascade, starting with the phosphorylation of the JNKK, Hemipterous (HEP). This binds to a scaffolding

protein, Connector of kinase to AP-1 (CKA), bringing into close proximity the JNK protein, Basket (BSK) which is phosphorylated by HEP. CKA is also phosphorylated which results in the dissociation of BSK which translocates to the nucleus. Here it binds with a nuclear-residing CKA molecule which additionally recruits the AP-1 transcription factor consisting of the c-Jun orthologue, JRA, and the c-Fos orthologue, Kayak (KAY). BSK may phosphorylate both JRA and KAY which dissociate from CKA and activate transcription of genes involved in the early immune response thought to be involved in wound repair and stress mechanisms. Additionally, the gene responsible for encoding the phosphatase Puckered (PUC) is activated which is responsible for dephosphorylating BSK, an example of a negative regulatory loop.

The Imd pathway mediates the immune response against Gram-negative bacteria infection. During immune challenge, the JNK pathway is activated prior to the activation of the Imd pathway. This early immune response does not require REL activity, in fact, it has been proposed that the main target of the JNK pathway activation, the AP-1 transcription factor, inhibits the activation of REL dependent genes. However, once REL is activated the early response is terminated and a sustained immune response of the Imd pathway is active.

In addition to these core components, many new gene products have been linked to the Imd pathway but their function have not been fully established:

- Amidase PGRPs: Recently, it has been shown that the Imd pathway is down-regulated by the amidase PGRPs, PGRP-LB and PGRP-SC1. They exert their action extracellularly by scavenging peptidoglycan into non-immune stimulatory fragments.
- PGRP-LE: PGRP-LE participates with PGRP-LC in the sensing of DAP-PGN and may play a role in the sensing of monomeric PGN in the cytosol.
- PGRP-LF: PGRP-LF appears to block PGRP-LC-mediated activation of the Imd/JNK pathway possibly by interaction with PGRP-LC at the plasma membrane or by sequestering PGN away from PGRP-LC (Maillet et al., 2008).
- Negative regulators of the Imd pathway: CASPAR, Plenty of SH3s (POSH).
- SCF complex components may be involved in the processing of REL: SKPA, Cullin1 (LIN19), and Slimb (SLMB) (Khush et al., 2002).
- Components of the ubiquitin E3 ligase complex: Bendless (BEN) and UEV1A (Zhou et al., 2005).
- JNK: The Imd pathway can activate the JNK pathway, through the JNKK Hemipterous (HEP), at the level of TAK1 (Boutros et al., 2002; Silverman et al., 2003).
- Nuclear factor Akirin (aka Bhringi (BHR)) (Goto et al., 2008) and GATA zinc finger transcription factor, Serpent (SRP) (Senger et al., 2004) synergize with Relish (REL) and activate transcription.

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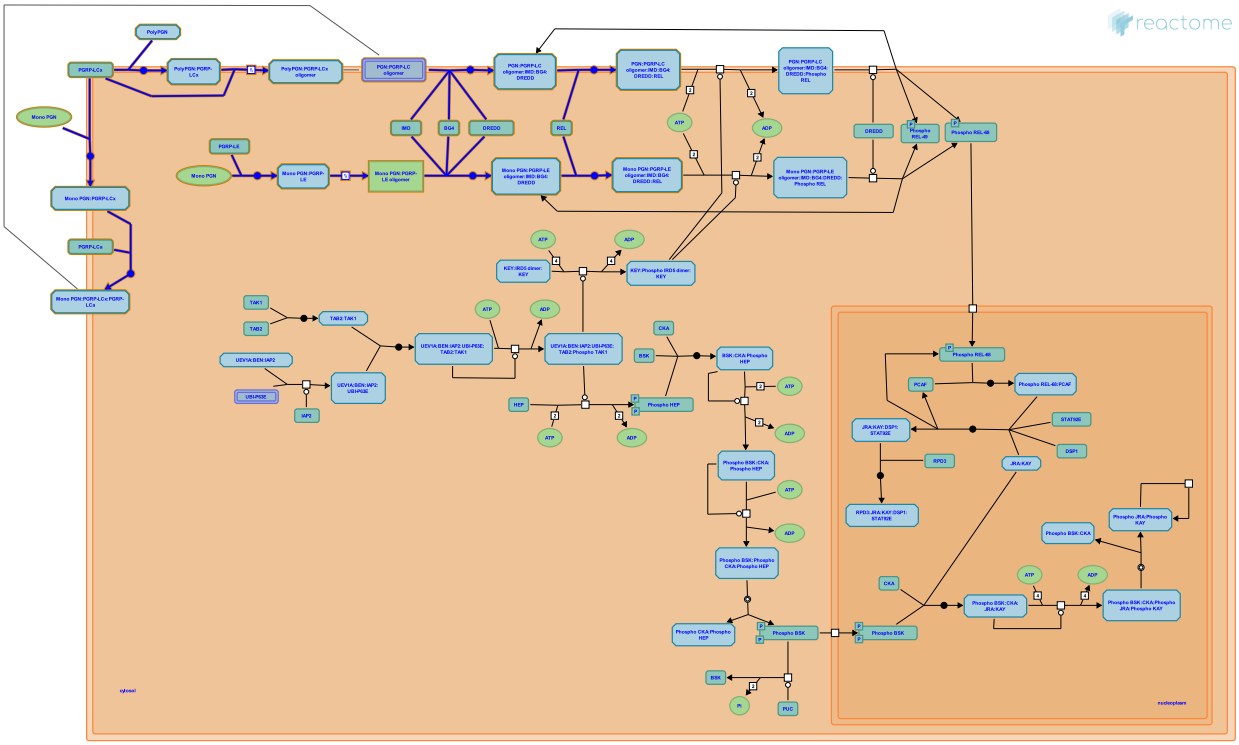
Editions

2007-07-11	Authored, Edited	Williams, MG.
2008-06-20	Reviewed	Lemaitre, B., Silverman, N.

Formation of the PGN:PGRP-LC/LE receptor 'signalling complex' ↗

Location: Imd pathway

Stable identifier: R-DME-209438



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Leclerc, V., Reichhart, JM. (2004). The immune response of Drosophila melanogaster. *Immunol Rev, 198*, 59-71. ↗

Editions

2007-07-11	Authored	Williams, MG.
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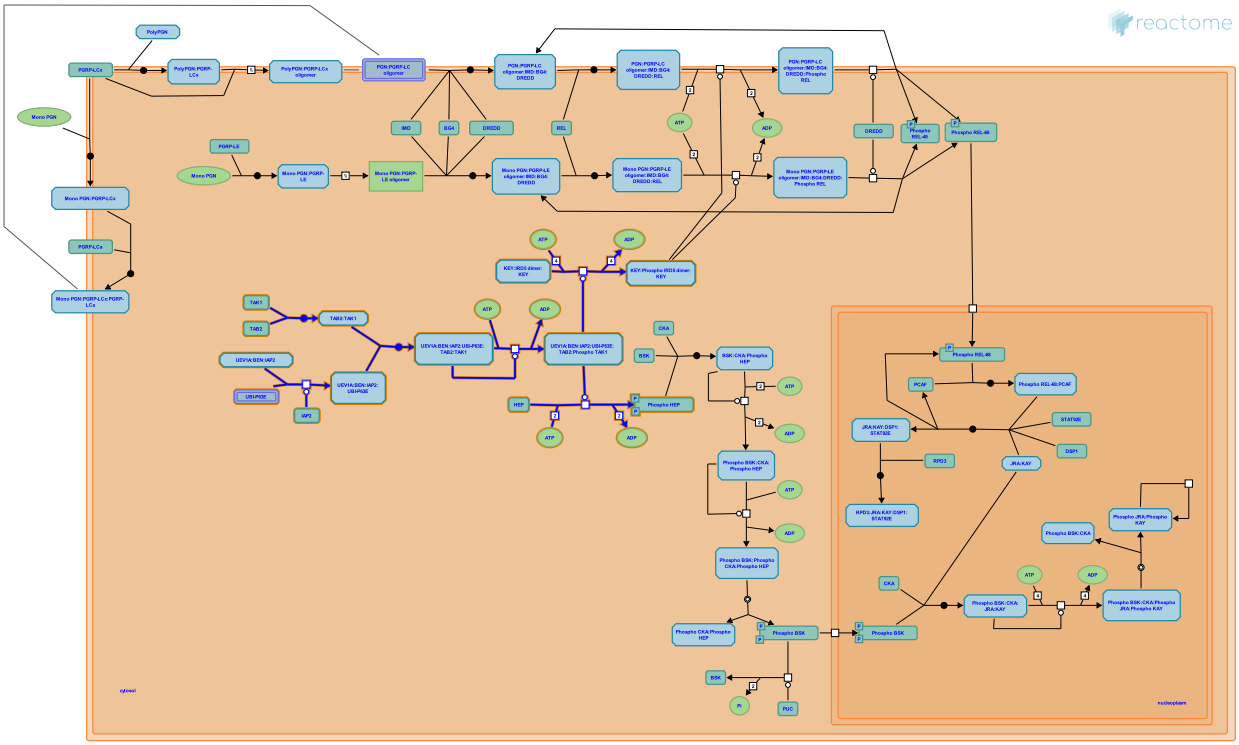
Activation of the IkappaB kinase complex, KEY:IRD5 dimer:KEY ↗

Location: Imd pathway

Stable identifier: R-DME-209447



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2007-07-11	Authored	Williams, MG.
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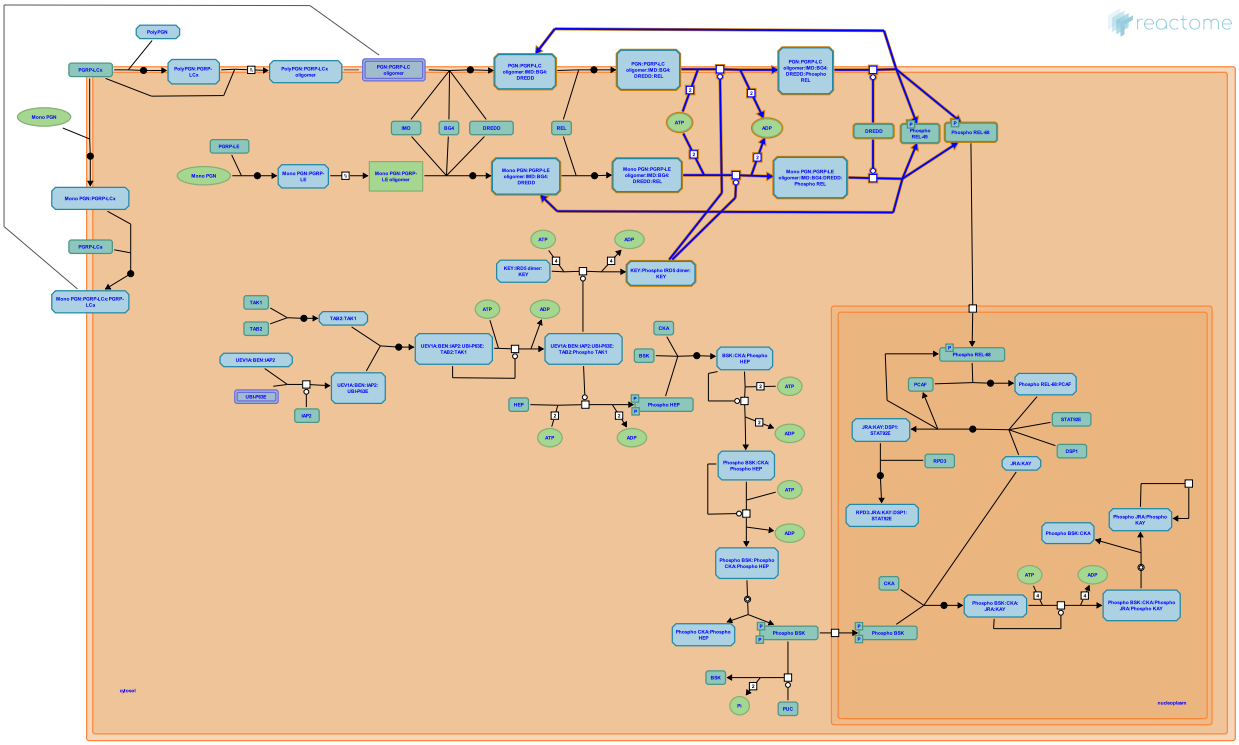
Catalytic processing of the nuclear factor, REL ↗

Location: Imd pathway

Stable identifier: R-DME-209465



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2007-07-11	Authored	Williams, MG.
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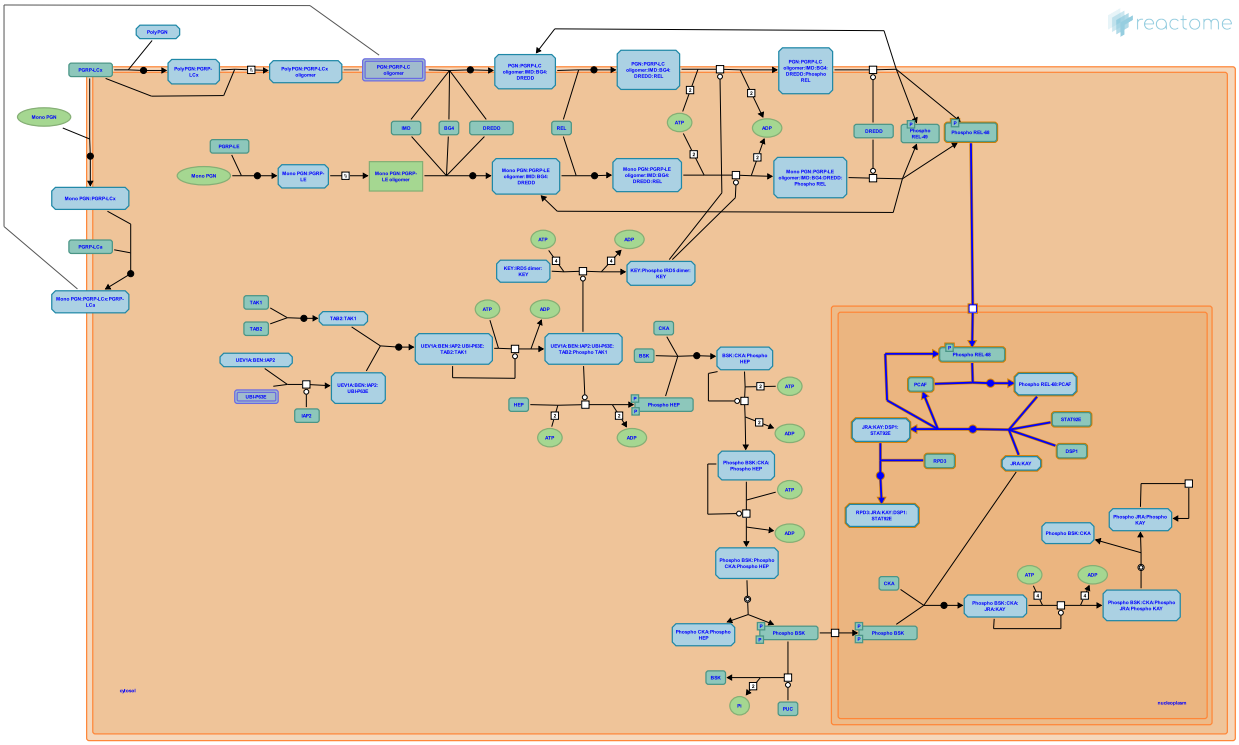
Transcriptional activtion and repression of REL-68 target genes

Location: Imd pathway

Stable identifier: R-DME-209394



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

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Editions

2007-07-11	Authored	Williams, MG.
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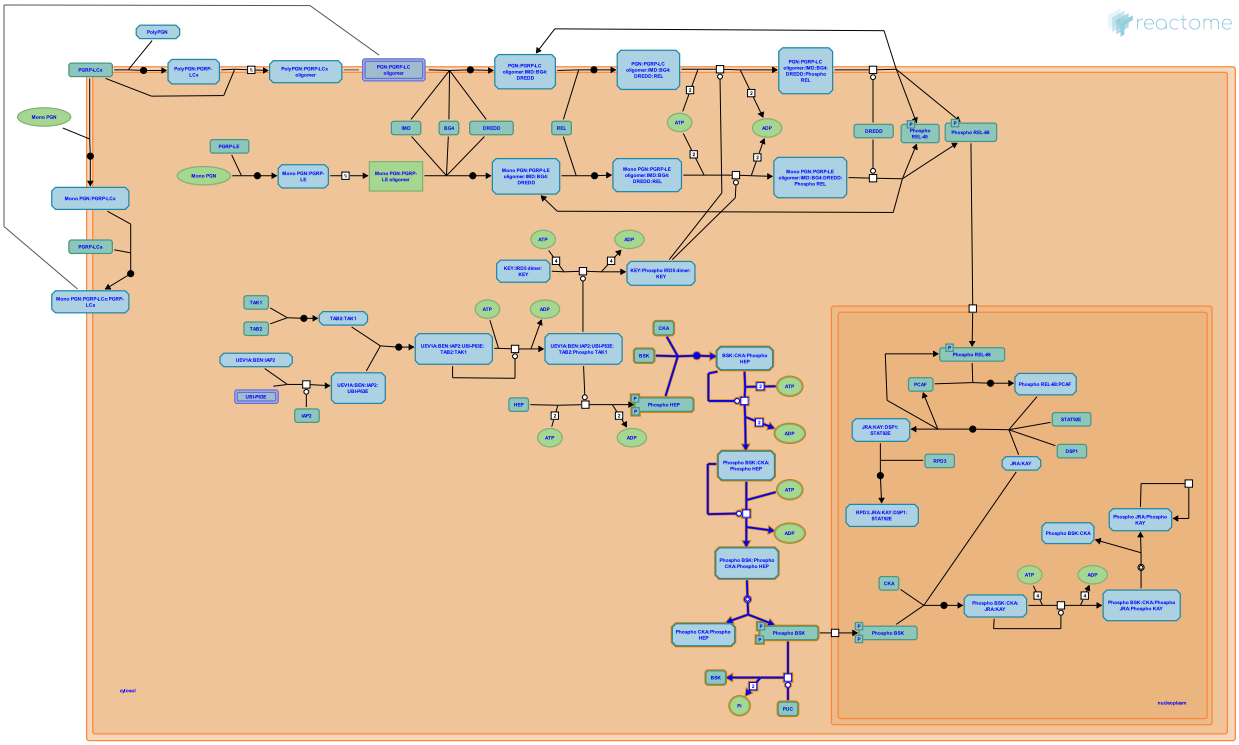
Formation of the cytosolic BSK 'scaffolding complex'

Location: Imd pathway

Stable identifier: R-DME-209397



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Leclerc, V., Reichhart, JM. (2004). The immune response of Drosophila melanogaster. *Immunol Rev, 198*, 59-71.

Editions

2007-07-11	Authored	Williams, MG.
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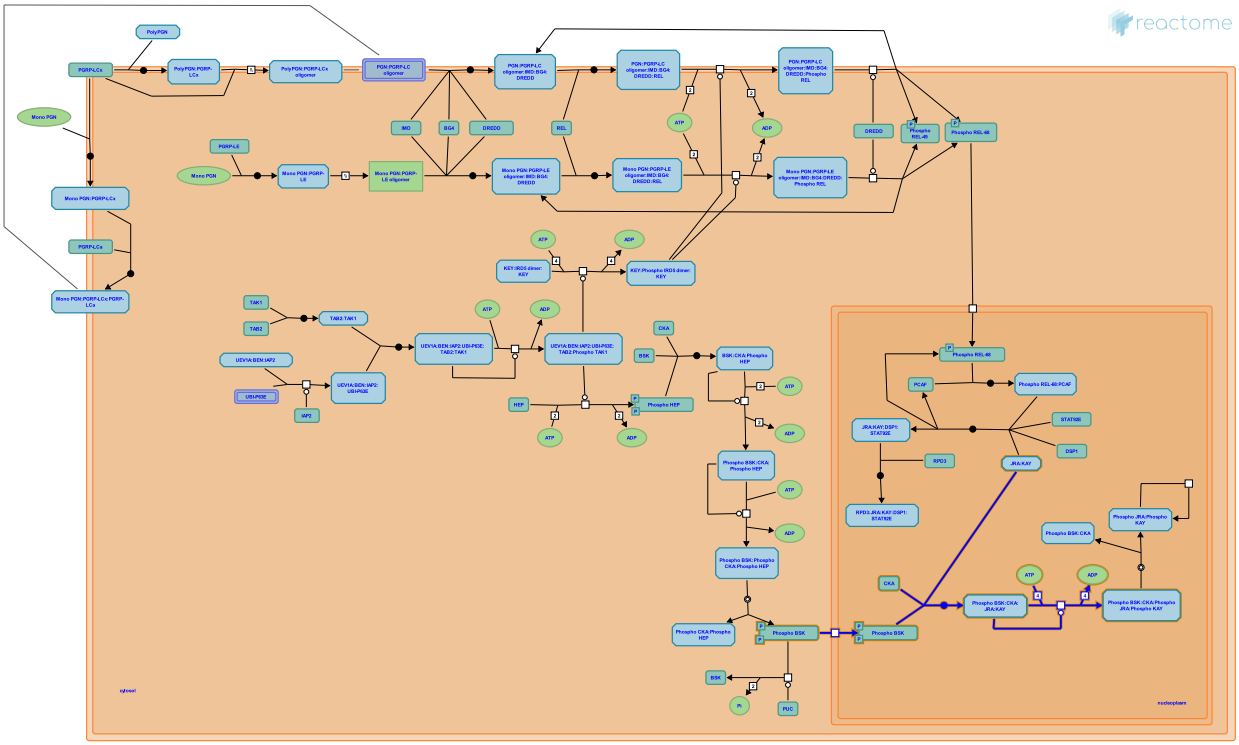
Formation of the nuclear AP-1 transcription factor 'scaffolding complex'

Location: Imd pathway

Stable identifier: R-DME-209409



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Leclerc, V., Reichhart, JM. (2004). The immune response of Drosophila melanogaster. *Immunol Rev, 198*, 59-71.

Editions

2007-07-11	Authored	Williams, MG.
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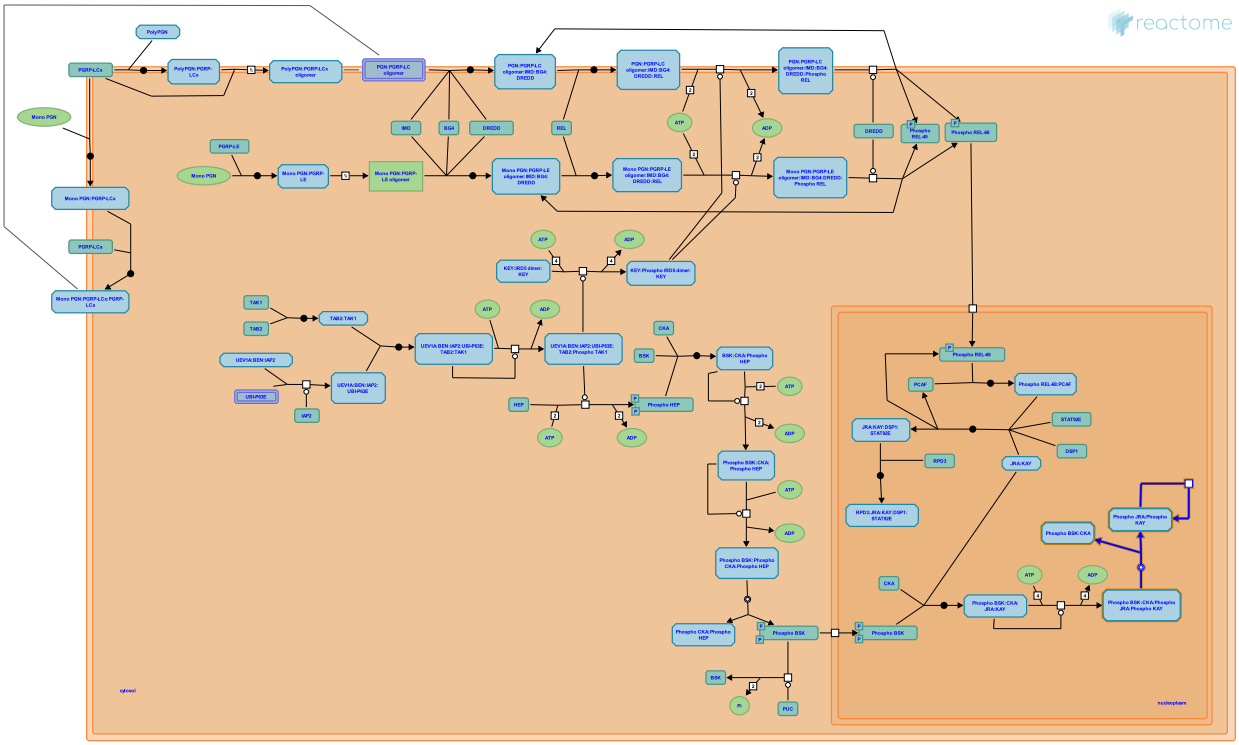
Transcriptional activtion by AP-1 transcription factor ↗

Location: Imd pathway

Stable identifier: R-DME-209425



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Leclerc, V., Reichhart, JM. (2004). The immune response of Drosophila melanogaster. *Immunol Rev, 198*, 59-71. ↗

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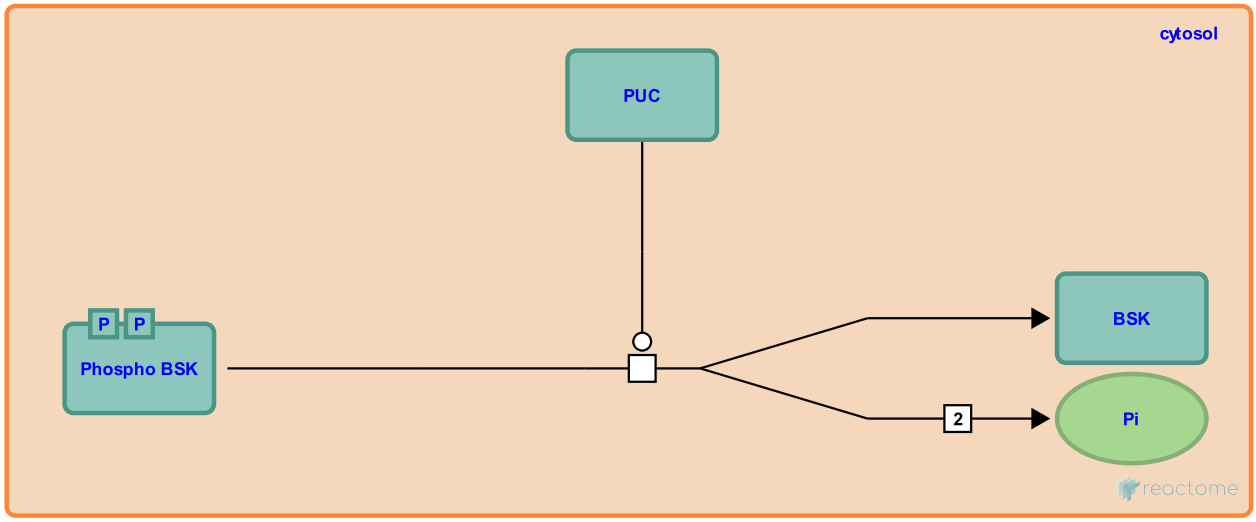
Phosphorylated BSK kinase is dephosphorylated and deactivated by PUC phosphatase ↗

Location: Imd pathway

Stable identifier: R-DME-209157

Type: transition

Compartments: cytosol



The JUN kinase phosphatase Puckered (PUC) dephosphorylates and consequently deactivates the phosphorylated Basket (BSK) kinase. The gene that encodes PUC is a target of the AP-1 transcription factor making this interaction part of a regulatory negative feedback loop.

Literature references

Martinez-Arias, A., Tolkovsky, AM., Gampel, A., Ring, J., Virdee, K., Kirov, N. et al. (1998). puckered encodes a phosphatase that mediates a feedback loop regulating JNK activity during dorsal closure in Drosophila. *Genes Dev, 12,* 557-70. ↗

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