Toll pathway

Lemaitre, B., Silverman, N., Williams, MG.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

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.

17/11/2022
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


Reactome database release: 82

This document contains 4 pathways (see Table of Contents)
In Drosophila, the Toll pathway establishes the embryonic dorsoventral axis and triggers innate immune responses to infection, along with the Imd pathway.

The Toll pathway plays a key role in the response to Gram-positive cocci and Fungi by regulating a large set of genes (including antimicrobial peptide genes, many small peptides with unknown function as well as components of the melanization and clotting cascades) by the fat body and in hemocytes that circulate in the hemolymph (De Gregorio et al., 2002). The canonical component of the Toll pathway contains: Spatzle (SPZ), Toll (TL), Pelle (PLL), Tube (TUB), MYD88, Cactus (CACT), Dorsal (DL), Dorsal-related immunity factor (DIF) (Belvin et al., 1996; Tauszig-Delamasure et al., 2002). Many other functions have been proposed for the Toll pathway including hemocyte differentiation (Evans et al., 2003; Meister, 2004), muscle attachment and motoneuron defects (Halfon et al., 1995).

The Toll pathway is activated after the cleavage of SPZ by serine protease cascades. The proteolytic cascade activating SPZ during dorsoventral patterning has been well delineated and involves the serine proteases: Gastrulation defective (GD); Snake (SNK); and Easter (EA), that directly cleave the full-length Spatzle (SPZ) dimer ligand. This cascade is negatively regulated by the serpin SPN27A that acts at the level of EA (Dissing et al., 2001; LeMosy et al., 2001). The cascades activating SPZ during the immune response are much more complex with branches involved in the sensing of Glucan found in fungi (through GNBP3) or Lysine-type peptidoglycans (PGNs) found in gram positive cocci (through PGRP-SA, GNBP1 and PGRP-SD) and via the serine protease, Persephone (PSH), in the sensing of entomopathogenic fungus via the detection of protease. These proteolytic cascades which are not yet well characterised converge and lead to activation of Spatzle-processing enzyme (SPE) that cleave Spatzle in the hemolymph.

The processed SPZ dimer binds to the extracellular part of the Toll (TL) receptor at the plasma membrane. This causes TL to activate and dimerise through its cytoplasmic domains. In response to this activity, the adaptor proteins MYD88, Tube (TUB), and the Ser/Thr kinase Pelle (PLL) are recruited to the TL receptor cytoplasmic region to form the 'signalling complex'. In addition, during dorsoventral patterning in the embryo, the zinc-finger adaptor protein, Weckle (WEK) forms an extra link between MYD88 and the TL receptor (Chen et al., 2006). PLL is activated, autophosphorylates and recruits the...
DL/DIF dimer, complexed to the NF-kappaB inhibitor orthologue, Cactus (CACT) to the 'signalling complex'. CACT is complexed to NF-kappaB orthologue dimers of either Dorsal (DL) in dorsoventral polarity and larvae immune response or Dorsal-related immunity factor, Dif (DIF), the main transcription factor in the innate immunity response. The next stage is unclear but it is believed that PLL or an unknown kinase tentatively labelled the 'Cactus kinase' phosphorylate CACT and the DL/DIF dimer. CACT in complex with the DL/DIF dimer dissociates from the 'signalling complex'. The phosphorylated CACT is degraded probably by the 26S proteasome, and the now free phosphorylated DL/DIF dimer translocates to the nucleus to activate transcription of genes encoding a battery of antimicrobial peptides in the immune response or genes that organise dorsoventral patterning.

**Literature references**


Formation of the trans-membrane 'signalling complex'

Location: Toll pathway

Stable identifier: R-DME-209442

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

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007-07-11</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2007-07-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2008-06-20</td>
<td>Reviewed</td>
<td>Lemaitre, B., Silverman, N.</td>
</tr>
</tbody>
</table>
Degradation of NF-kappa-B inhibitor, CACT

Location: Toll pathway

Stable identifier: R-DME-209406

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

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007-07-11</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2007-07-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2008-06-20</td>
<td>Reviewed</td>
<td>Lemaitre, B., Silverman, N.</td>
</tr>
</tbody>
</table>
Transcriptional activtion by phosphorylated DL/DIF dimer

**Location:** Toll pathway

**Stable identifier:** R-DME-209400

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

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007-07-11</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2007-07-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2008-06-20</td>
<td>Reviewed</td>
<td>Lemaitre, B., Silverman, N.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

- Toll pathway 2
  - Formation of the trans-membrane 'signalling complex' 4
  - Degradation of NF-kappa-B inhibitor, CACT 5
  - Transcriptional activation by phosphorylated DL/DIF dimer 6

Table of Contents 7