Listeria monocytogenes entry into host cells

Orlic-Milacic, M., Schwerk, C.
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: 72

This document contains 3 pathways (see Table of Contents)
Listeria monocytogenes entry into host cells

Stable identifier: R-HSA-8876384

Diseases: listeriosis

Listeria monocytogenes is a short, gram-positive, nonspore-forming motile rod. Serotypes 1/2a, 1/2b and 4b make up more than 95% of isolates from humans, with serotype 4b causing most of the food-borne outbreaks. Listeria monocytogenes enters the body through the gastrointestinal tract after ingestion of contaminated food. The bacteria can survive food preservation procedures, such as refrigeration, low pH and high salt.

Listeria monocytogenes expresses several adhesin proteins at the cell surface that facilitate bacterial binding and entry to host cells. The bacteria can enter host cells through endocytosis mediated by binding of the bacterial InlA (internalin) protein to CDH1 (E-cadherin) at the host cell plasma membrane. Listeria monocytogenes can also enter host cells through endocytosis mediated by binding of the bacterial InlB protein to MET receptor tyrosine kinase at the host cell plasma membrane. Listeria monocytogenes proliferates inside the host cells and triggers formation of filopods, elongated protrusions of the host plasma membrane that contain bacteria. Filopods are ingested by adjacent cells, allowing Listeria monocytogenes to spread from cell to cell, invisible to the immune system of the host.

Listeria monocytogenes can cross the intestinal, blood-brain and placental barriers. In immunocompetent adults Listeria monocytogenes infection usually causes gastroenteritis. In infants infected in utero and in immunocompromised adults Listeria monocytogenes infection can result in meningoencephalitis and bacteremia (sepsis).

InlA is critical for crossing the intestinal barrier while both InlA and InlB are needed for crossing the placental barrier (Gessain et al. 2015) and, based on in vitro studies, the blood-cerebrospinal fluid barrier (Grundler et al. 2013). It seems that the intrinsic level of PI3K activity in Listeria-targeted host cells determines whether the entry depends on InlA only or InlA and InlB. The interaction of InlA with E-cadherin does not activate PI3K/AKT signaling while the interaction of InlB with the MET receptor activated the PI3K/AKT signal transduction cascade. Therefore, InlB-MET interaction may be important in tissues with low intrinsic PI3K activity (Gessain et al. 2015). Even if InlA-E-cadherin route is sufficient for bacterial entry, InlB may accelerate bacterial invasion (Pentecost et al. 2010). Cholesterol levels in host cell plasma membrane may also influence the preferred route for bacterial endocytosis (Seveau et al. 2004). In addition to InlA and InlB, many other virulence factors are involved in the Listeria monocytogenes infection cycle (Camejo et al. 2011) and will be annotated as mechanistic details become available.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-06-14</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-10-25</td>
<td>Reviewed</td>
<td>Schwerk, C.</td>
</tr>
<tr>
<td>2016-10-26</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
InlA-mediated entry of *Listeria monocytogenes* into host cells

**Location:** *Listeria monocytogenes* entry into host cells

**Stable identifier:** R-HSA-8876493

**Diseases:** listeriosis

The pathogenic bacteria *Listeria monocytogenes* can enter host cells through endocytosis triggered by binding of the bacterial cell wall protein internalin (InlA) to the E-cadherin (CDH1) complex at the host cell plasma membrane (Mengaud et al. 1996, Lecuit et al. 1999). Binding of InlA to CDH1, similar to CDH1 engagement during normal cell-to-cell adhesion, triggers activation of the SRC protein tyrosine kinase and phosphorylation of CDH1 and CDH1-bound beta-catenin (CTNNB1) (Fujita et al. 2002, McLachlan et al. 2007, Sousa et al. 2007, Bonazzi et al. 2008). Integrins likely contribute to CDH1-triggered SRC activation, and ERKs (MAPK1 and MAPK3), ROCKs and MLCK may also be involved (Avizienyte et al. 2002, Avizienyte et al. 2004, Martinez-Rico et al. 2010). FAK1 (PTK2), a SRC-regulated protein tyrosine kinase, may contribute to SRC-mediated regulation of CDH1 (Avizienyte et al. 2002).

Phosphorylation of CDH1 and CTNNB1 by SRC creates docking sites for a CBL-like ubiquitin protein ligase Hakai (CBLL1). CBLL1 ubiquitinates SRC-phosphorylated CDH1 and CTNNB1 upon InlA binding, as well as in the context of CDH1-mediated cell-to-cell adhesion, thus triggering CDH1 endocytosis (Fujita et al. 2002, Bonazzi et al. 2008, Mukherjee et al. 2012).

CBLL1 may also undergo SRC-mediated phosphorylation and subsequent autoubiquitination (Fujita et al. 2002).

Both clathrin-mediated and caveolin-mediated endocytosis are implicated in the InlA-mediated entry of *Listeria monocytogenes* to host cells (Veiga et al. 2007). SRC-mediated phosphorylation of cortactin and the ARP2/3 complex involved in actin polymerization is implicated in CDH1 endocytosis and *Listeria monocytogenes* internalization (Sousa et al. 2007, Ren et al. 2009).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-06-14</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-10-25</td>
<td>Reviewed</td>
<td>Schwerk, C.</td>
</tr>
<tr>
<td>2016-10-26</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
InlB-mediated entry of Listeria monocytogenes into host cell

**Location:** Listeria monocytogenes entry into host cells

**Stable identifier:** R-HSA-8875360

**Diseases:** listeriosis

InlB, a cell wall protein of Listeria monocytogenes, binds MET receptor, acting as an HGF agonist (Shen et al. 2000, Veiga and Cossart 2005). Listeria monocytogenes InlB proteins dimerize through their leucine-rich repeat regions (LRRs), promoting dimerization of MET receptors that they are bound to (Ferraris et al. 2010). InlB-induced MET receptor dimerization is followed by MET trans-autophosphorylation and activation of downstream RAS/RAF/MAPK signaling and PI3K/AKT signaling (Niemann et al. 2007, Ferraris et al. 2010). InlB-bound phosphorylated MET receptor recruits the E3 ubiquitin ligase CBL through GRB2. CBL-mediated monoubiquitination of InlB-bound MET promotes endocytosis and entry of Listeria monocytogenes to host cells (Veiga and Cossart 2005). CIN85 is necessary for endocytosis-mediated entry of Listeria monocytogenes triggered by CBL-mediated monoubiquitination of MET (Veiga and Cossart 2005). Proteins involved in clathrin-mediated endocytosis EPS15 and HGS (Hrs) are both necessary for CBL and MET-mediated entry of Listeria monocytogenes into host cells (Veiga and Cossart 2005).

A potential coreceptor role of CD44 in InlB-mediated MET activation is contradictory (Jung et al. 2009, Dortet et al. 2010).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-06-14</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-10-25</td>
<td>Reviewed</td>
<td>Schwerk, C.</td>
</tr>
<tr>
<td>2016-10-26</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction

Listeria monocytogenes entry into host cells

InlA-mediated entry of Listeria monocytogenes into host cells

InlB-mediated entry of Listeria monocytogenes into host cell

Table of Contents