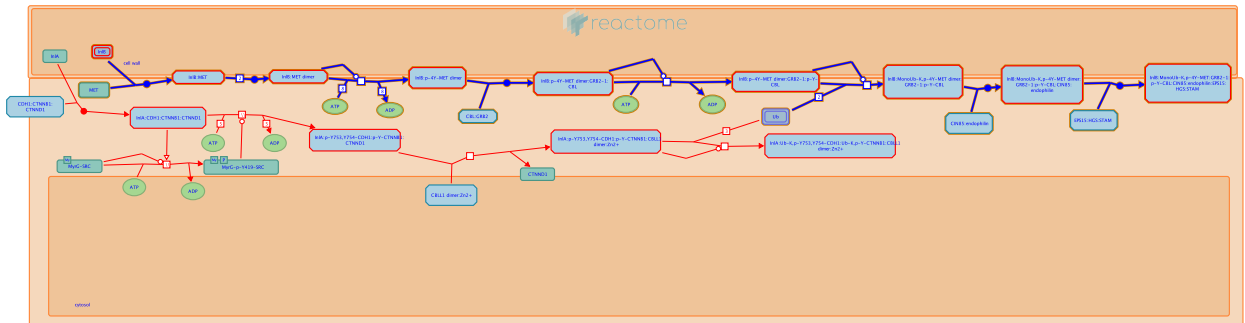


InlB-mediated entry of *Listeria monocytogenes* into host cell



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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.

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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. [↗](#)
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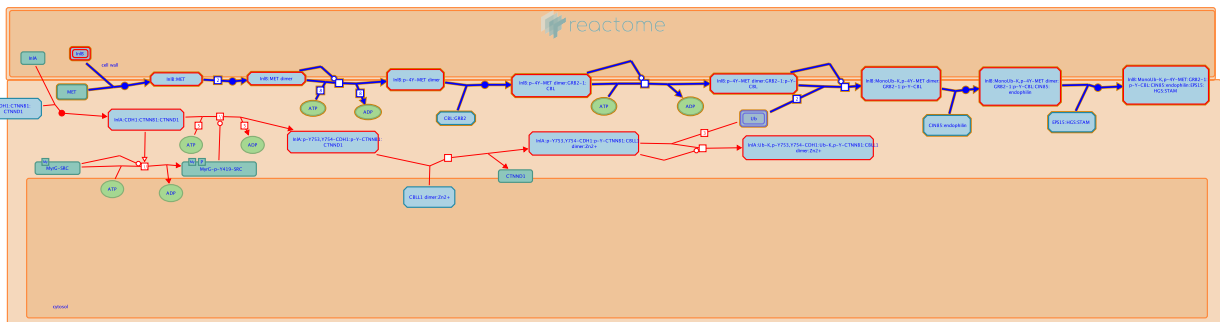
Reactome database release: 77

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

InIB-mediated entry of *Listeria monocytogenes* into host cell ↗

Stable identifier: R-HSA-8875360

Diseases: listeriosis



InIB, 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* InIB proteins dimerize through their leucine-rich repeat regions (LRRs), promoting dimerization of MET receptors that they are bound to (Ferraris et al. 2010). InIB-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). InIB-bound phosphorylated MET receptor recruits the E3 ubiquitin ligase CBL through GRB2. CBL-mediated monoubiquitination of InIB-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 InIB-mediated MET activation is contradictory (Jung et al. 2009, Dortet et al. 2010).

Literature references

- Jung, C., Matzke, A., Niemann, HH., Schwerk, C., Tenenbaum, T., Orian-Rousseau, V. (2009). Involvement of CD44v6 in InIB-dependent *Listeria* invasion. *Mol. Microbiol.*, 72, 1196-207. ↗
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- Shen, Y., Naujokas, M., Park, M., Ireton, K. (2000). InIB-dependent internalization of *Listeria* is mediated by the Met receptor tyrosine kinase. *Cell*, 103, 501-10. ↗
- Veiga, E., Cossart, P. (2005). *Listeria* hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. *Nat. Cell Biol.*, 7, 894-900. ↗

Editions

2016-06-14	Authored	Orlic-Milacic, M.
2016-10-25	Reviewed	Schwerk, C.
2016-10-26	Edited	Orlic-Milacic, M.

InIB binds MET ↗

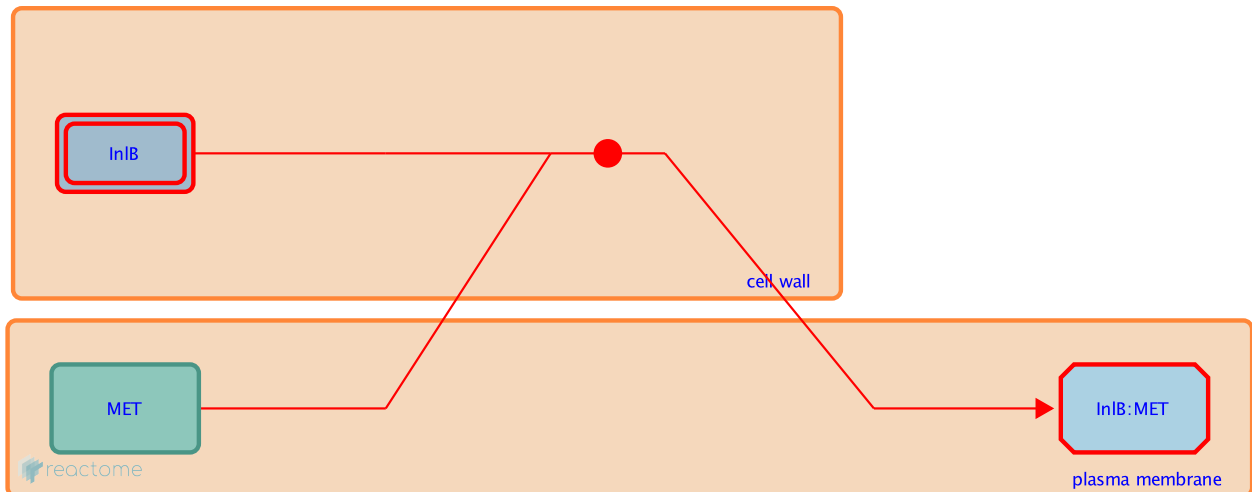
Location: [InIB-mediated entry of *Listeria monocytogenes* into host cell](#)

Stable identifier: R-HSA-8875371

Type: binding

Compartments: cell wall, plasma membrane

Diseases: listeriosis



InIB, a cell wall protein of *Listeria monocytogenes*, binds MET receptor, acting as an HGF agonist. InIB interacts with the extracellular portion of MET via two interfaces: the leucine rich repeat region (LRR) of InIB interacts with the Ig1 repeat of MET, while the inter-repeat (IR) region of InIB interacts with the Sema domain of MET (Shen et al. 2000, Veiga and Cossart 2005, Niemann et al. 2007).

Followed by: [InIB promotes MET dimerization](#)

Literature references

Veiga, E., Cossart, P. (2005). *Listeria* hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. *Nat. Cell Biol.*, 7, 894-900. ↗

Shen, Y., Naujokas, M., Park, M., Ireton, K. (2000). InIB-dependent internalization of *Listeria* is mediated by the Met receptor tyrosine kinase. *Cell*, 103, 501-10. ↗

Niemann, HH., Jäger, V., Butler, PJ., van den Heuvel, J., Schmidt, S., Ferraris, D. et al. (2007). Structure of the human receptor tyrosine kinase met in complex with the *Listeria* invasion protein InIB. *Cell*, 130, 235-46. ↗

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InIB promotes MET dimerization ↗

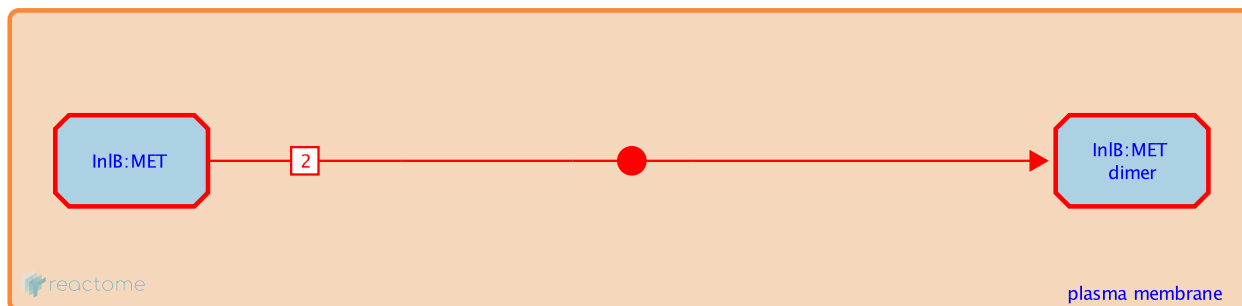
Location: [InIB-mediated entry of *Listeria monocytogenes* into host cell](#)

Stable identifier: R-HSA-8876210

Type: binding

Compartments: plasma membrane, cell wall

Diseases: listeriosis



Listeria monocytogenes InIB proteins dimerize through their leucine-rich repeat regions (LRRs), promoting dimerization of their associated MET receptors (Ferraris et al. 2010).

Preceded by: [InIB binds MET](#)

Followed by: [InIB:MET dimer trans-autophosphorylates](#)

Literature references

Ferraris, DM., Gherardi, E., Di, Y., Heinz, DW., Niemann, HH. (2010). Ligand-mediated dimerization of the Met receptor tyrosine kinase by the bacterial invasion protein InIB. *J. Mol. Biol.*, 395, 522-32. ↗

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InlB:MET dimer trans-autophosphorylates ↗

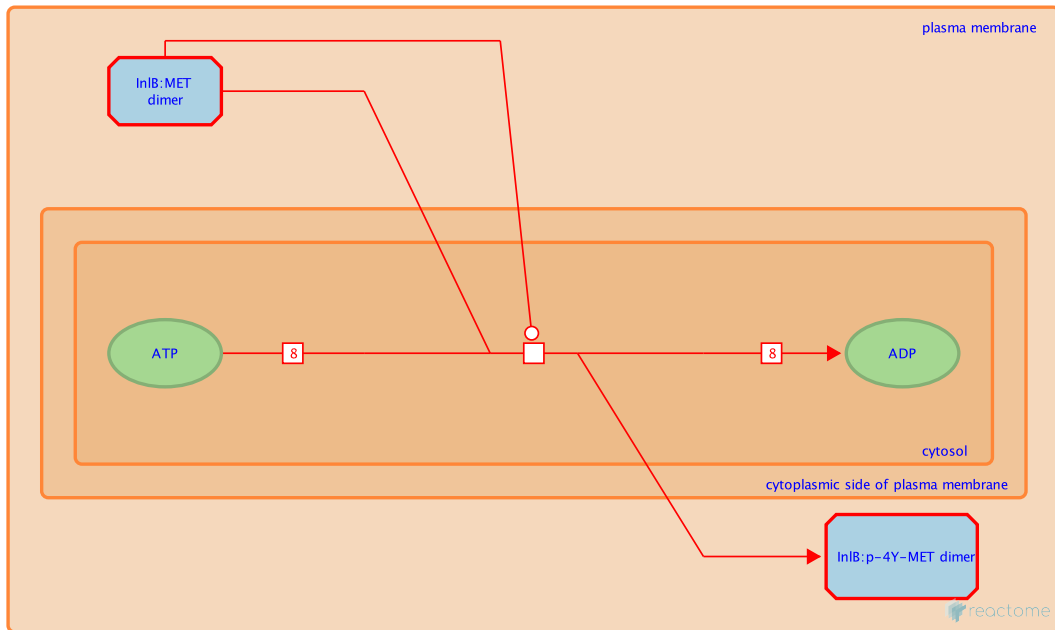
Location: [InlB-mediated entry of *Listeria monocytogenes* into host cell](#)

Stable identifier: R-HSA-8876230

Type: transition

Compartments: cytosol, plasma membrane, cell wall

Diseases: listeriosis



MET bound to *Listeria monocytogenes* InlB protein undergoes trans-autophosphorylation. Phosphorylation at tyrosine residues Y1234 and Y1235 in the activation loop of the kinase domain of MET was specifically demonstrated. As InlB-activated MET activates downstream signaling by ERKs (MAPKs) and PI3K/AKT, MET is presumably phosphorylated on GRB2 and GAB1 docking sites Y1349 and Y1356, respectively (Niemann et al. 2007, Ferraris et al. 2010).

Preceded by: [InlB promotes MET dimerization](#)

Followed by: [CBL binds InlB-activated MET](#)

Literature references

Ferraris, DM., Gherardi, E., Di, Y., Heinz, DW., Niemann, HH. (2010). Ligand-mediated dimerization of the Met receptor tyrosine kinase by the bacterial invasion protein InlB. *J. Mol. Biol.*, 395, 522-32. ↗

Niemann, HH., Jäger, V., Butler, PJ., van den Heuvel, J., Schmidt, S., Ferraris, D. et al. (2007). Structure of the human receptor tyrosine kinase met in complex with the *Listeria* invasion protein InlB. *Cell*, 130, 235-46. ↗

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CBL binds InlB-activated MET ↗

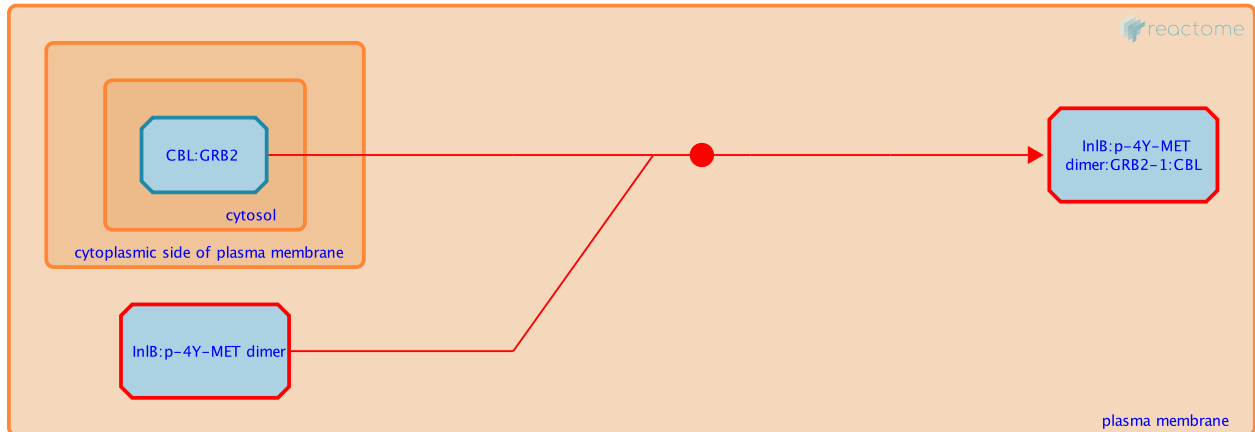
Location: [InlB-mediated entry of Listeria monocytogenes into host cell](#)

Stable identifier: R-HSA-8876240

Type: binding

Compartments: plasma membrane, cell wall, cytosol

Diseases: listeriosis



GRB2 is needed for the recruitment of CBL to the complex of Listeria monocytogenes InlB protein and phosphorylated MET receptor (Veiga and Cossart 2005).

Preceded by: [InlB:MET dimer trans-autophosphorylates](#)

Followed by: [InlB-activated MET phosphorylates CBL](#)

Literature references

Veiga, E., Cossart, P. (2005). Listeria hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. *Nat. Cell Biol.*, 7, 894-900. ↗

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InlB-activated MET phosphorylates CBL ↗

Location: InlB-mediated entry of *Listeria monocytogenes* into host cell

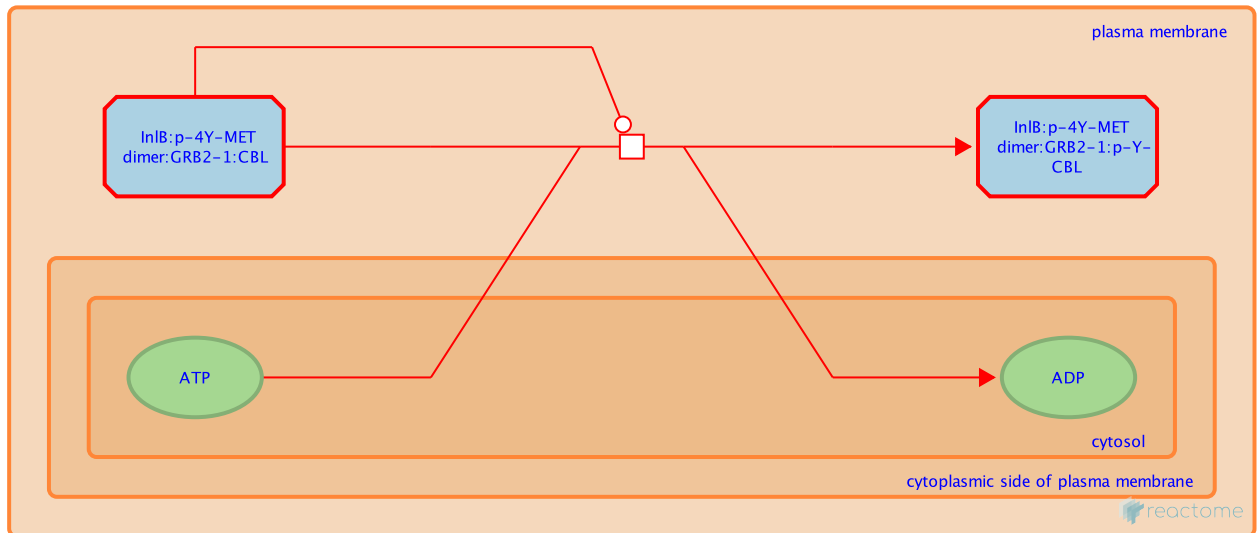
Stable identifier: R-HSA-8876246

Type: transition

Compartments: plasma membrane, cell wall, cytosol

Diseases: listeriosis

Inferred from: MET phosphorylates CBL (Homo sapiens)



Binding of InlB to MET receptor induces CBL phosphorylation on tyrosine residue(s). Based on the analogy with HGF-induced MET signaling, MET receptor activated by binding of the *Listeria monocytogenes* protein InlB phosphorylates CBL, promoting stronger interaction of CBL with MET (Peschard et al. 2001, Petrelli et al. 2002).

Preceded by: CBL binds InlB-activated MET

Followed by: CBL monoubiquitinates InlB-bound MET

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2016-06-14	Authored	Orlic-Milacic, M.
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CBL monoubiquitinates InIB-bound MET ↗

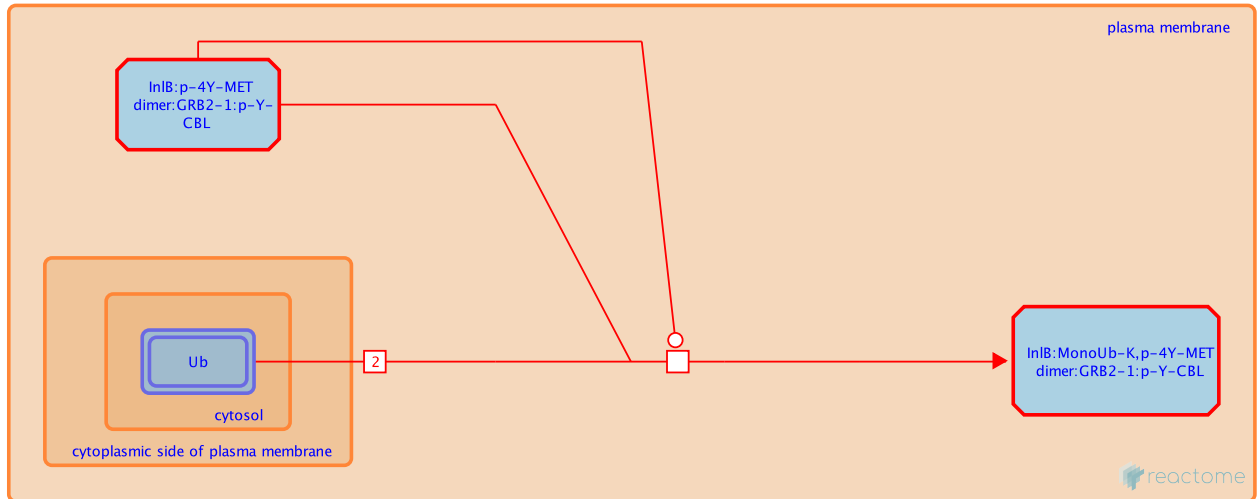
Location: [InIB-mediated entry of Listeria monocytogenes into host cell](#)

Stable identifier: R-HSA-8876258

Type: transition

Compartments: plasma membrane, cell wall, cytosol

Diseases: listeriosis



CBL promotes monoubiquitination of MET receptor that is activated by binding of the Listeria monocytogenes cell wall protein InIB. CBL-mediated monoubiquitination of MET promotes endocytosis and entry of Listeria monocytogenes into host cells (Veiga and Cossart 2005).

Preceded by: [InIB-activated MET phosphorylates CBL](#)

Followed by: [CBL recruits CIN85:endophilin complex to InIB-bound MET](#)

Literature references

Veiga, E., Cossart, P. (2005). Listeria hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. *Nat. Cell Biol.*, 7, 894-900. ↗

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CBL recruits CIN85:endophilin complex to InIb-bound MET ↗

Location: InIb-mediated entry of *Listeria monocytogenes* into host cell

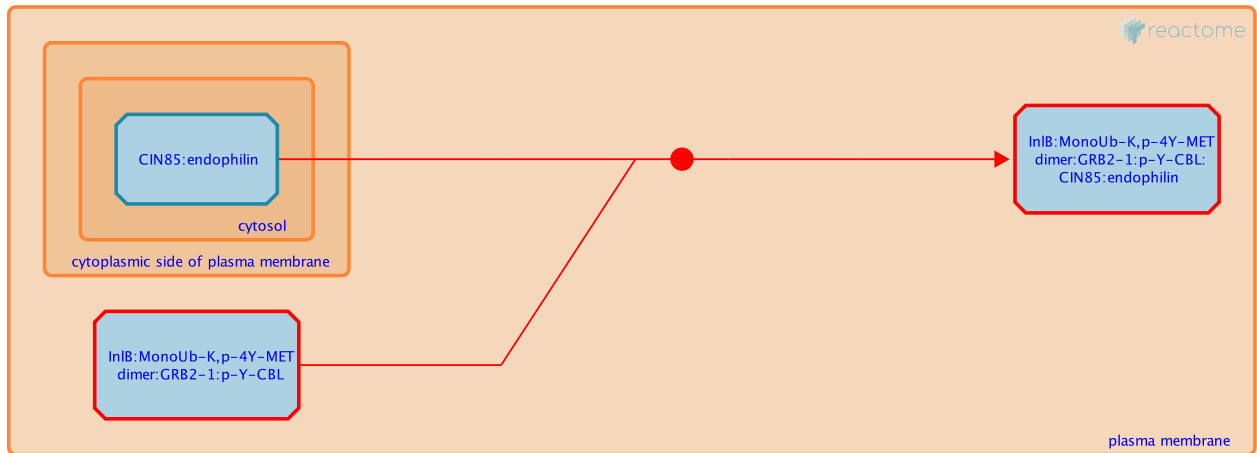
Stable identifier: R-HSA-8876255

Type: binding

Compartments: plasma membrane, cell wall, cytosol

Diseases: listeriosis

Inferred from: CBL recruits CIN85:endophilin to ubiquitinated MET (Homo sapiens)



CIN85 is necessary for endocytosis-mediated entry of *Listeria monocytogenes* triggered by CBL-mediated monoubiquitination of MET receptor activated by binding to the bacterial cell wall protein InIb (Veiga et al. 2005). Based on the analogy with HGF-activated MET signaling (Petrelli et al. 2002), CBL recruits the complex of CIN85 and endophilin to *Listeria*-engaged MET.

Preceded by: CBL monoubiquitinates InIb-bound MET

Followed by: EPS15 and HGS bind CBL-monoubiquitinated MET engaged with *Listeria* InIb

Literature references

Veiga, E., Cossart, P. (2005). *Listeria* hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. *Nat. Cell Biol.*, 7, 894-900. ↗

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EPS15 and HGS bind CBL-monoubiquitinated MET engaged with Listeria InlB ↗

Location: [InlB-mediated entry of Listeria monocytogenes into host cell](#)

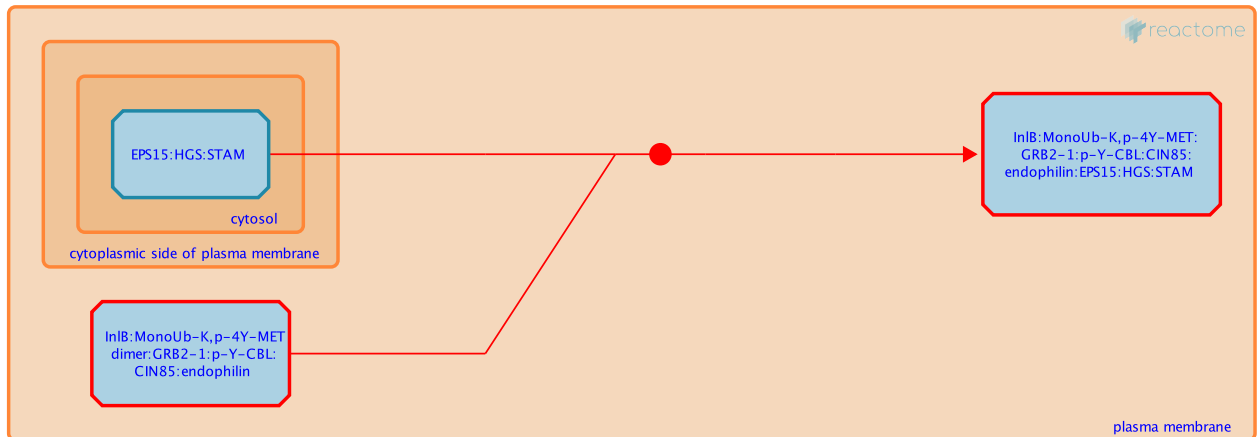
Stable identifier: R-HSA-8876262

Type: binding

Compartments: plasma membrane, cell wall, cytosol

Diseases: listeriosis

Inferred from: [EPS15 and HGS bind ubiquitinated MET \(Homo sapiens\)](#)



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). Based on the analogy with HGF-activated MET signaling (Bache et al. 2003, Row et al. 2005, Parachoniak et al. 2009), HGS and EPS15, in complex with STAM proteins, bind to MET receptor monoubiquitinated by CBL upon MET receptor activation by the Listeria monocytogenes InlB protein.

Preceded by: [CBL recruits CIN85:endophilin complex to InlB-bound MET](#)

Literature references

Veiga, E., Cossart, P. (2005). Listeria hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. *Nat. Cell Biol.*, 7, 894-900. ↗

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