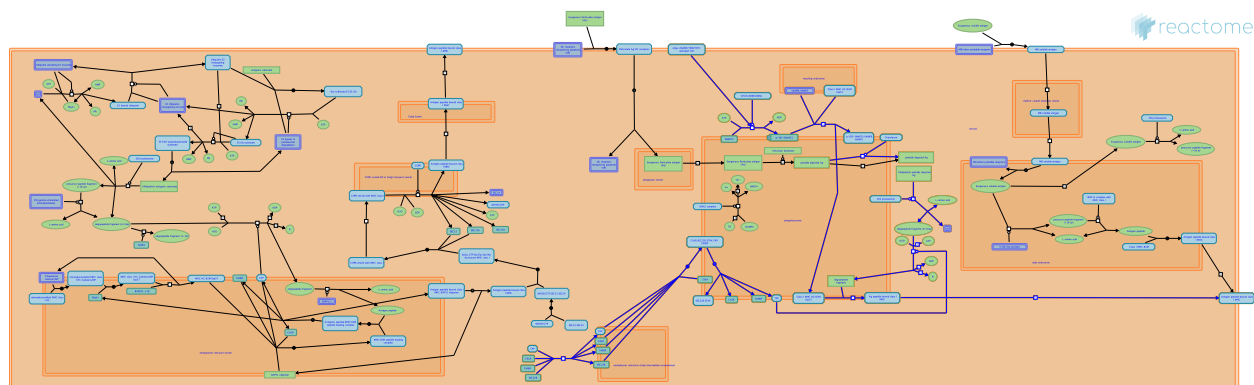


ER-Phagosome pathway



Bergeron, JJ., Desjardins, M., English, L., Garapati, P V., Jupe, S.

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

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08/09/2021

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

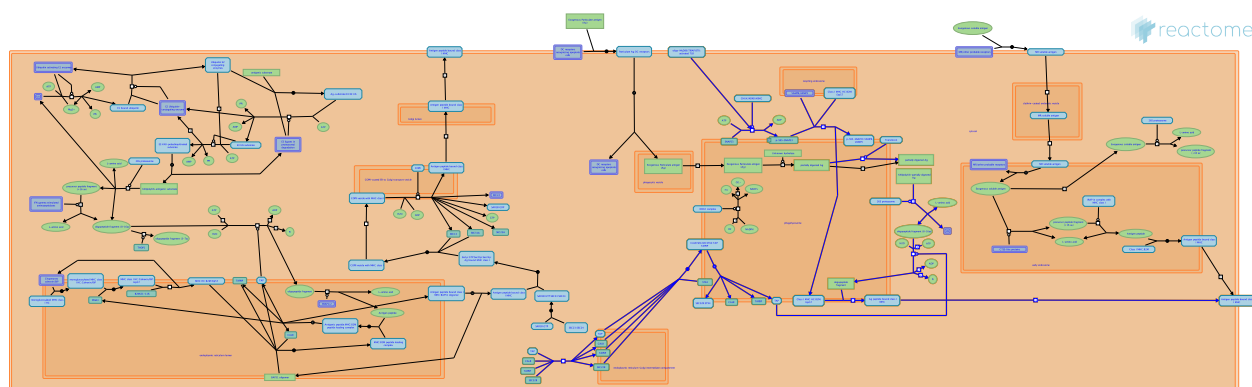
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Reactome database release: 77

This document contains 1 pathway and 10 reactions ([see Table of Contents](#))

ER-Phagosome pathway ↗

Stable identifier: R-HSA-1236974



The other TAP-dependent cross-presentation mechanism in phagocytes is the endoplasmic reticulum (ER)-phagosome model. Desjardins proposed that ER is recruited to the cell surface, where it fuses with the plasma membrane, underneath phagocytic cups, to supply membrane for the formation of nascent phagosomes (Gagnon et al. 2002). Three independent studies simultaneously showed that ER contributes to the vast majority of phagosome membrane (Guermonprez et al. 2003, Houde et al. 2003, Ackerman et al. 2003). The composition of early phagosome membrane contains ER-resident proteins, the components required for cross-presentation. This model is similar to the phagosome-to-cytosol model in that Ag is translocated to cytosol for proteasomal degradation, but differs in that antigenic peptides are translocated back into the phagosome (instead of ER) for peptide:MHC-I complexes. ER fusion with phagosome introduces molecules that are involved in Ag transport to cytosol (Sec61) and proteasome-generated peptides back into the phagosome (TAP) for loading onto MHC-I.

Although the ER-phagosome pathway is controversial, the concept remains attractive as it explains how peptide-receptive MHC-I molecules could intersect with a relatively high concentration of exogenous antigens, presumably a crucial prerequisite for efficient cross-presentation (Basha et al. 2008).

Literature references

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Editions

2011-03-28	Authored, Edited	Garapati, P V.
2011-05-13	Reviewed	Desjardins, M., English, L.
2016-05-16	Reviewed	Bergeron, JJ.

Egress of internalized antigen to the cytosol via sec61 [↗](#)

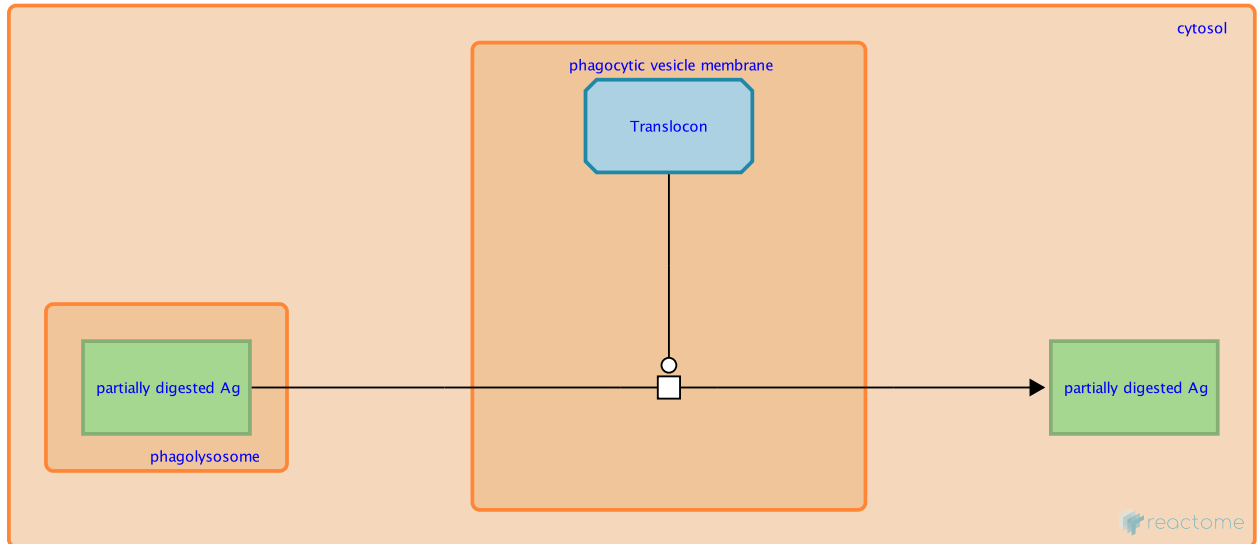
Location: [ER-Phagosome pathway](#)

Stable identifier: R-HSA-1236947

Type: transition

Compartments: phagocytic vesicle membrane, cytosol, phagolysosome

Inferred from: [Egress of internalized antigen to the cytosol via sec61 \(Gallus gallus\)](#)



Fusion of the maturing phagosome with the ER mediates the exchange of materials resulting in the formation of a hybrid ER-phagosome compartment (Gagnon et al. 2002, Guermonprez et al. 2003, Houde et al. 2003, Ackerman et al. 2003, Blanchard et al. 2010). This hybrid contains the retrotranslocon factor Sec61 that mediates the access of proteasomes on the cytosolic surface of the phagosome. Using fluorescence imaging, Houde et al. (2003) provided evidence for the role of Sec61 in the retrotranslocation of internalized exogenous proteins from phagosomes to the cytoplasmic face of J774 macrophages. Sec61 factor is a heterotrimeric complex composed of alpha, beta and gamma subunits forming the core of the mammalian ER translocon (Greenfield et al. 1999). Oligomers of the Sec61 complex form a transmembrane channel involved in the retrotranslocation of misfolded proteins from ER to the cytosol for degradation, and thus it has been proposed that Sec61 might be involved in the translocation of proteins in phagosomes to the cytosol (Kasturi et al. 2008).

Followed by: [Proteasomal cleavage of substrate](#)

Editions

2011-03-28	Authored, Edited	Garapati, P V.
2011-05-13	Reviewed	Desjardins, M., English, L.

Proteasomal cleavage of substrate ↗

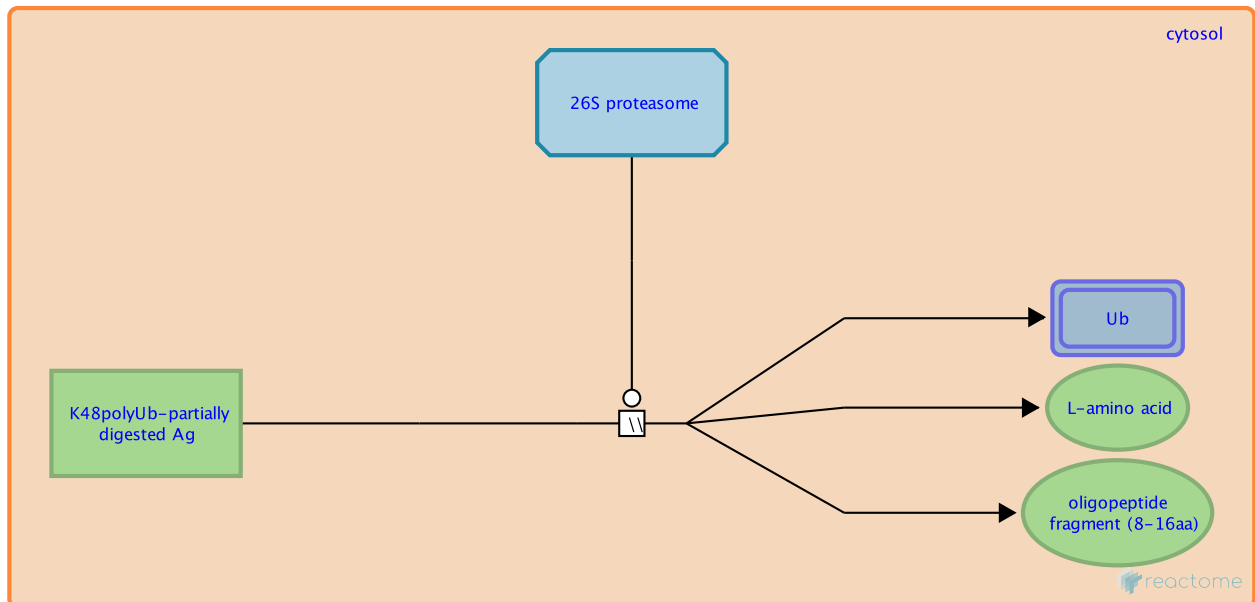
Location: ER-Phagosome pathway

Stable identifier: R-HSA-1236935

Type: omitted

Compartments: cytosol

Inferred from: Proteasomal cleavage of ovalbumin (OVA) (Gallus gallus)



Proteasomes are usually localized to the cytoplasm but are also present in the nucleus and ER. Houde et al. (2003) investigated the distribution of proteasomes in J774 macrophages and observed them on phagosomes. The proteasomes present on phagosomes may not come directly from ER, but instead assemble on phagosomes to play a function at a precise point during phagolysosomal biogenesis. Houde et al. also observed polyubiquitinated proteins on the cytoplasmic side of phagosomes and highlighted the link between the ubiquitination process and proteasomal degradation; translocated peptides are ubiquitinated and processed by the proteasome complex assembled on the cytoplasmic side of phagosomes, leading to the generation of MHC class I binding peptides.

Preceded by: Egress of internalized antigen to the cytosol via sec61

Followed by: Translocation of antigenic peptides back to phagosomes via TAP

Editions

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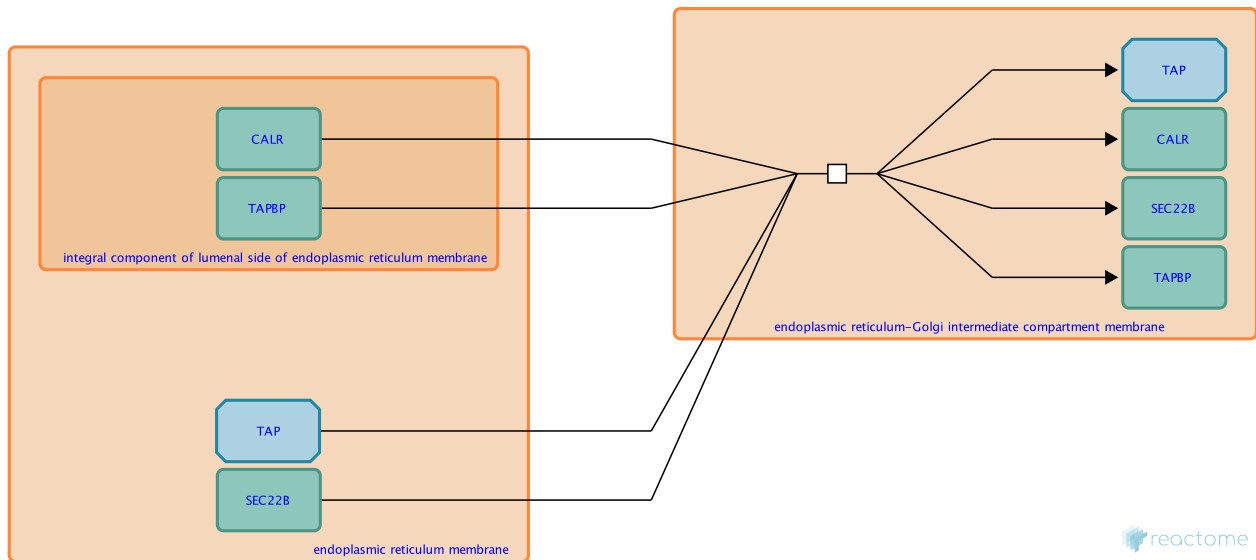
Transport of SEC22B, TAP and PLC from ER to ERGIC ↗

Location: ER-Phagosome pathway

Stable identifier: R-HSA-8863914

Type: transition

Compartments: endoplasmic reticulum-Golgi intermediate compartment membrane, endoplasmic reticulum membrane, integral component of luminal side of endoplasmic reticulum membrane



In DCs subset of ER proteins including MHC-I peptide loading complex (PLC) and transporter associated with antigen processing (TAP) transit to phagosomes via the intermediate compartment ER-Golgi intermediate compartment (ERGIC) (Cebrian et al. 2011). TAP exits the ER in COPII vesicles in association with MHC class I, and that peptide translocation by TAP and binding to class I can occur in post-ER compartments (Ghanem et al. 2010). SEC22B, an ER-resident SNARE is required for the transport of PLC from ERGIC (Cebrian et al. 2011), but this step does not deliver MHC-I (Nair-Gupta et al. 2014). Instead, MHC-I are recruited from an endosomal recycling compartment (ERC), which is marked by Rab11a, VAMP3/cellubrevin, and VAMP8/endobrevin that holds large reserves of MHC-I. This step is dependent on TLR signalling (Nair-Gupta et al. 2014).

Followed by: SEC22B, CALR, STX4, TAP and TAPBP bind

Literature references

Cebrian, I., Visentin, G., Blanchard, N., Jouve, M., Bobard, A., Moita, C. et al. (2011). Sec22b regulates phagosomal maturation and antigen crosspresentation by dendritic cells. *Cell*, 147, 1355-68. ↗

Nair-Gupta, P., Baccarini, A., Tung, N., Seyffer, F., Florey, O., Huang, Y. et al. (2014). TLR signals induce phagosomal MHC-I delivery from the endosomal recycling compartment to allow cross-presentation. *Cell*, 158, 506-21. ↗

Editions

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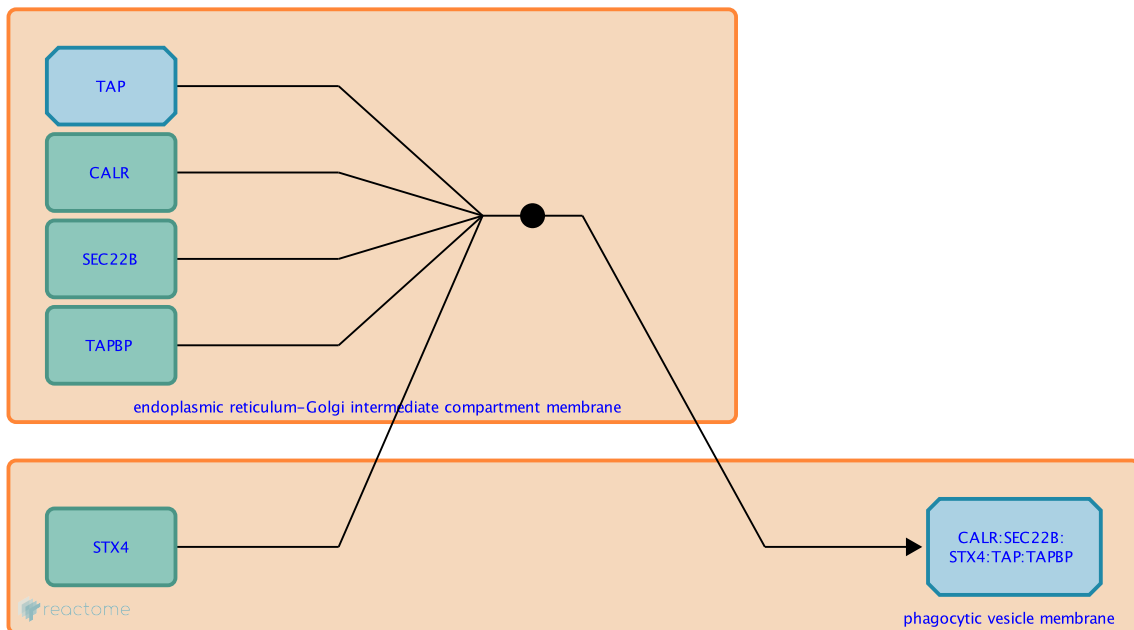
SEC22B, CALR, STX4, TAP and TAPBP bind ↗

Location: ER-Phagosome pathway

Stable identifier: R-HSA-8863858

Type: binding

Compartments: endoplasmic reticulum-Golgi intermediate compartment membrane, phagocytic vesicle membrane



The interaction between the two compartments could involve either direct fusion of ER stacks to phagosomes (Phgs) or vesicular intermediates. In both cases, a fusion event between the ER or ER-derived membrane vesicles and Phgs must occur. The SNARE SEC22B localizes to the ER-Golgi intermediate compartment (ERGIC) and interacts with SNARE syntaxin 4 (STX4) on phagosomes (Phgs), mediating the recruitment of subset of ER components including transporter associated with antigen processing (TAP), to phagosomes (Cebrian et al. 2011).

Preceded by: Transport of SEC22B, TAP and PLC from ER to ERGIC

Followed by: CALR, TAP, TAPBP dissociate from SEC22B:STX4

Literature references

Cebrian, I., Visentin, G., Blanchard, N., Jouve, M., Bobard, A., Moita, C. et al. (2011). Sec22b regulates phagosomal maturation and antigen crosspresentation by dendritic cells. *Cell*, 147, 1355-68. ↗

Editions

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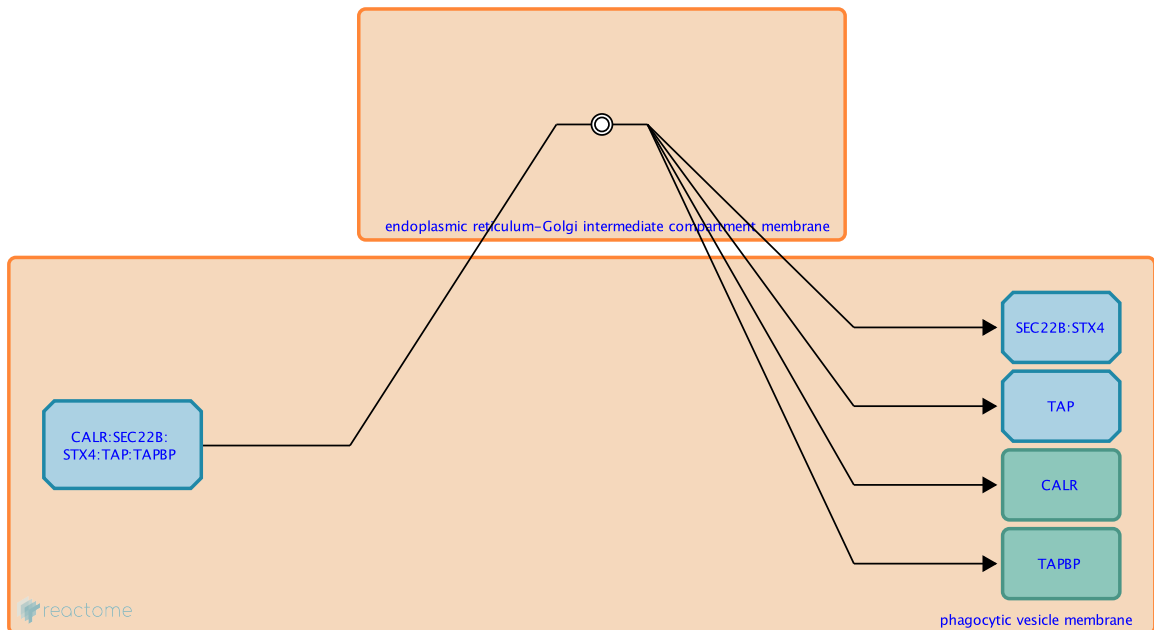
CALR, TAP, TAPBP dissociate from SEC22B:STX4 ↗

Location: ER-Phagosome pathway

Stable identifier: R-HSA-8951595

Type: dissociation

Compartments: endoplasmic reticulum-Golgi intermediate compartment membrane, phagocytic vesicle membrane



The interaction between the two compartments involves either direct fusion of ER stacks to phagosomes (Phgs) or vesicular intermediates. In both cases, a fusion event between the ER or ER-derived membrane vesicles and Phgs must occur. The SNARE SEC22B localizes to the ER-Golgi intermediate compartment (ERGIC) and interacts with SNARE syntaxin 4 (STX4) on phagosomes (Phgs), mediating the recruitment of subset of ER components including transporter associated with antigen processing (TAP), to phagosomes (Cebrian et al. 2011).

Preceded by: SEC22B, CALR, STX4, TAP and TAPBP bind

Followed by: Translocation of antigenic peptides back to phagosomes via TAP

Literature references

Cebrian, I., Visentin, G., Blanchard, N., Jouve, M., Bobard, A., Moita, C. et al. (2011). Sec22b regulates phagosomal maturation and antigen crosspresentation by dendritic cells. *Cell*, 147, 1355-68. ↗

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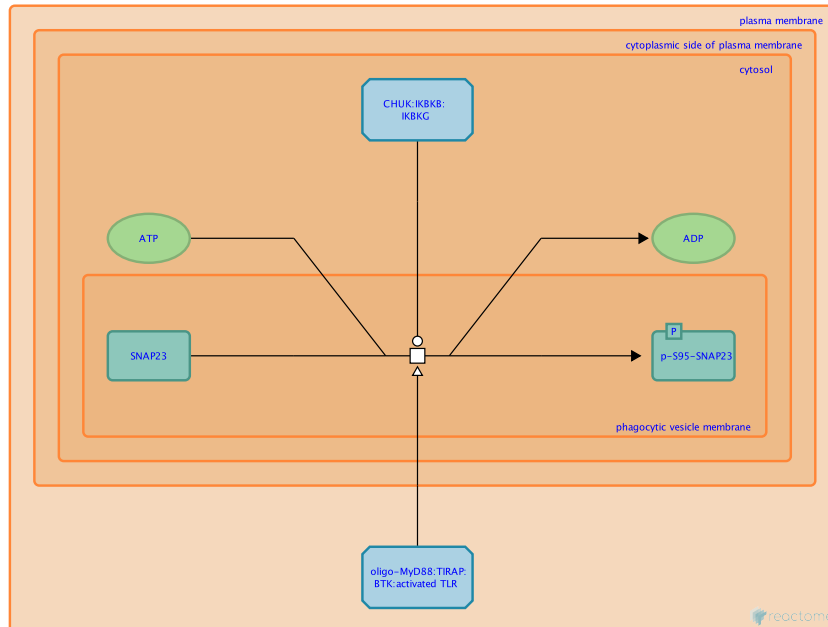
IKKB phosphorylates SNAP23 ↗

Location: ER-Phagosome pathway

Stable identifier: R-HSA-8863895

Type: transition

Compartments: phagocytic vesicle membrane, cytosol



A major reserve of MHC-I in dendritic cells reside within the endocytic recycling compartments (ERC). MHC-I trafficking to the ERC is regulated by the activity of Rab11a and subsequent trafficking from ERC to phagosomes is controlled by TLR-MyD88-IKK2-dependent phosphorylation of phagosomal SNAP23. Toll-like receptor (TLR) signalling regulate cross-presentation as they regulate phagocytosis and phagolysosomal fusion (Nair et al. 2011). MHC-I bearing ERC are enriched with R-SNAREs like RAB11a, VAMP3, and VAMP8. These SNARE molecules can interact with Q-SNARE SNAP23 present on phagosomes and this mediates membrane fusion. This interaction of SNAP23 with R-SNAREs require phosphorylation of SNAP23 (on Ser-95) by IKK2, and IKK2 is activated by TLR signalling. SNAP23 phosphorylation may increase SNAP23 binding to SNAREs. It may also regulate platelet and mast cell secretion (Karim et al. 2013, Suzuki & Verma 2008).

Followed by: [Fusion of ERC and phagosome](#)

Literature references

Nair-Gupta, P., Baccarini, A., Tung, N., Seyffer, F., Florey, O., Huang, Y. et al. (2014). TLR signals induce phagosomal MHC-I delivery from the endosomal recycling compartment to allow cross-presentation. *Cell*, 158, 506-21. ↗

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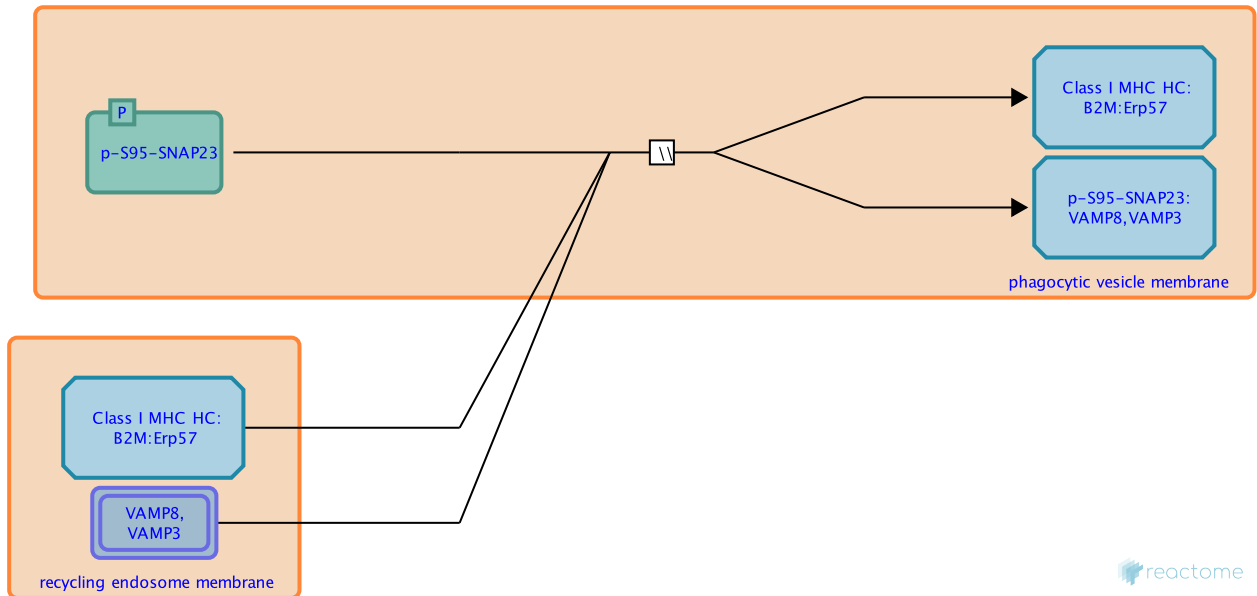
Fusion of ERC and phagosome ↗

Location: ER-Phagosome pathway

Stable identifier: R-HSA-8863973

Type: omitted

Compartments: phagocytic vesicle membrane, recycling endosome membrane



Recycling endosome-localized R-SNARE protein like RAB11a, VAMP3, and VAMP8 dock with target phagosome membrane Q-SNARE protein SNAP23. MHC-I present on the recycling endosomes would be delivered to phagosomes during this process.

Preceded by: IKKB phosphorylates SNAP23

Followed by: Peptide loading on MHC class I in phagosome

Literature references

Nair-Gupta, P., Baccarini, A., Tung, N., Seyffer, F., Florey, O., Huang, Y. et al. (2014). TLR signals induce phagosomal MHC-I delivery from the endosomal recycling compartment to allow cross-presentation. *Cell*, 158, 506-21. ↗

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Translocation of antigenic peptides back to phagosomes via TAP ↗

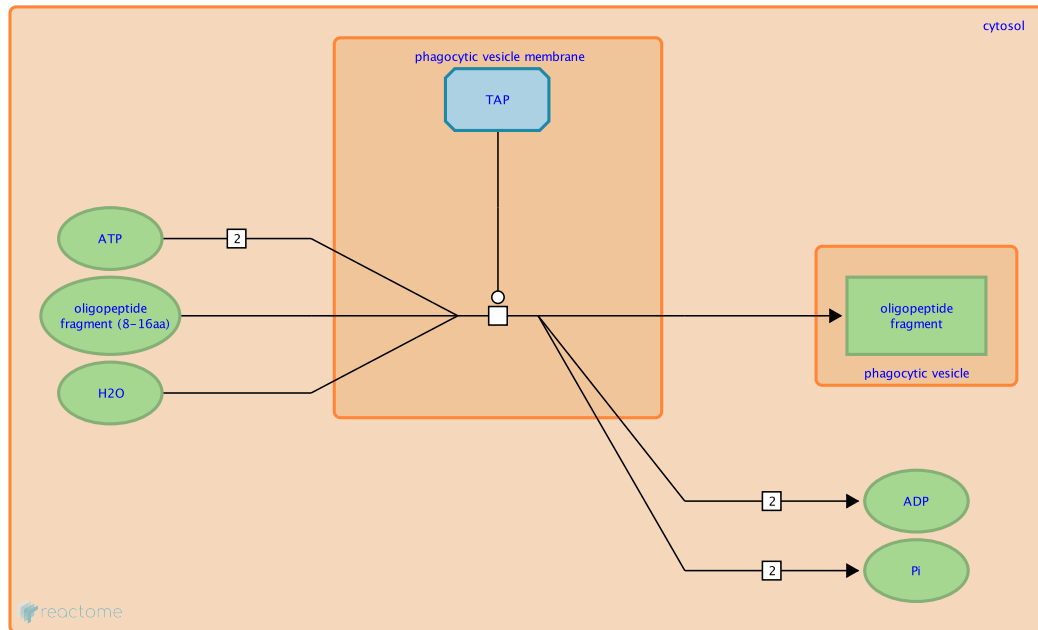
Location: ER-Phagosome pathway

Stable identifier: R-HSA-1236949

Type: transition

Compartments: phagocytic vesicle membrane, cytosol, phagocytic vesicle

Inferred from: [Translocation of antigenic peptides back to phagosomes via TAP \(Gallus gallus\)](#)



After processing by the proteasome, some of the oligopeptides could be reinternalized to the phagosome lumen of the same phagosome through the TAP complex probably acquired during ER-phagosome fusion. Guermónprez et al. (2003) tested this model and observed abundant TAP complex in early phagosomes and its reduction over time. Electron microscopy analysis of purified phagosomes also showed the insertion of TAP2 into the phagosomal membrane.

Preceded by: [Proteasomal cleavage of substrate](#), [CALR](#), [TAP](#), [TAPBP dissociate from SEC22B:STX4](#)

Followed by: [Peptide loading on MHC class I in phagosome](#)

Editions

2011-03-28	Authored, Edited	Garapati, P V.
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Peptide loading on MHC class I in phagosome ↗

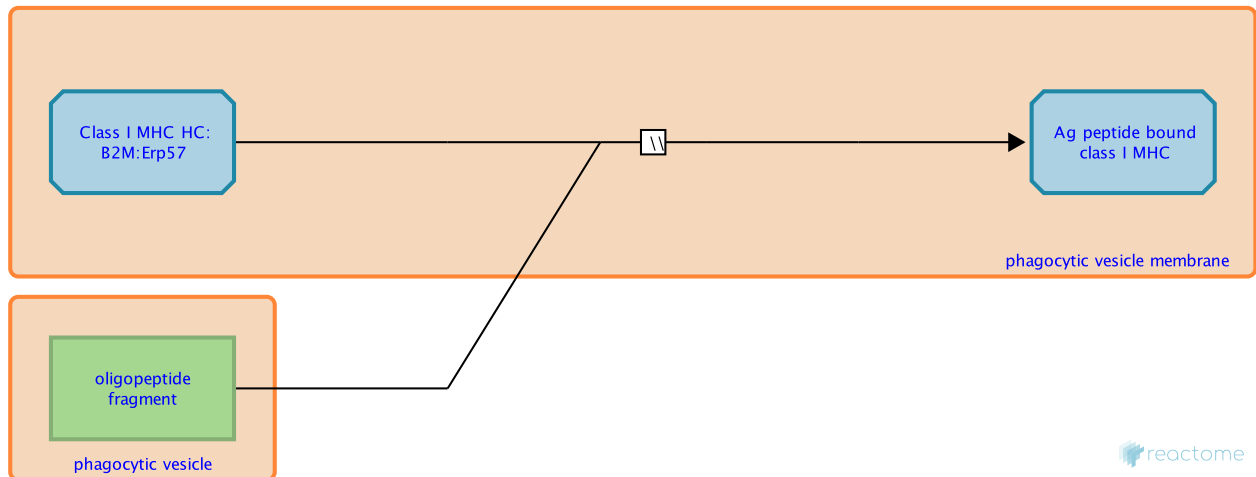
Location: [ER-Phagosome pathway](#)

Stable identifier: R-HSA-1236971

Type: omitted

Compartments: phagocytic vesicle membrane, phagocytic vesicle

Inferred from: [Peptide loading on MHC class I in phagosome \(Gallus gallus\)](#)



Peptides translocated back into the phagosomal lumen are loaded onto MHC class I molecules. Guernonprez et al. (2003) detected the components of the peptide loading complex (TAP, tapasin, calreticulin and Erp57) together with MHC class I in purified early phagosomes. They observed peptide loading in the presence of ATP in purified phagosomes expressing HLA-A2, incubated with iodinated S-9-L peptide. From these experiments they concluded that TAP-imported peptides can be loaded on MHC class I molecules in the lumen of phagosomes. Houde et al. (2003) also observed OVA peptide SIINFEKL:MHC-I complex in the phagosome lumen.

Preceded by: [Translocation of antigenic peptides back to phagosomes via TAP](#), [Fusion of ERC and phagosome](#)

Followed by: [Export of peptide loaded MHC class I complex to PM](#)

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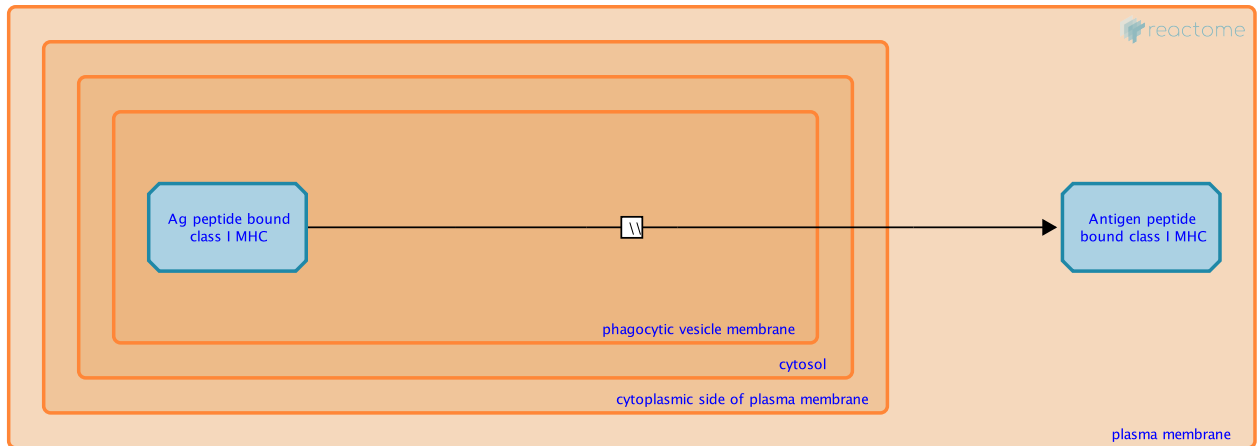
Export of peptide loaded MHC class I complex to PM [↗](#)

Location: [ER-Phagosome pathway](#)

Stable identifier: R-HSA-1236965

Type: omitted

Compartments: phagocytic vesicle membrane, plasma membrane



Exogenous antigen loaded class I MHC molecules in phagosomes may be delivered to the surface by membrane recycling machinery.

Preceded by: [Peptide loading on MHC class I in phagosome](#)

Literature references

Ramachandra, L., Simmons, D., Harding, CV. (2009). MHC molecules and microbial antigen processing in phagosomes. *Curr Opin Immunol*, 21, 98-104. [↗](#)

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