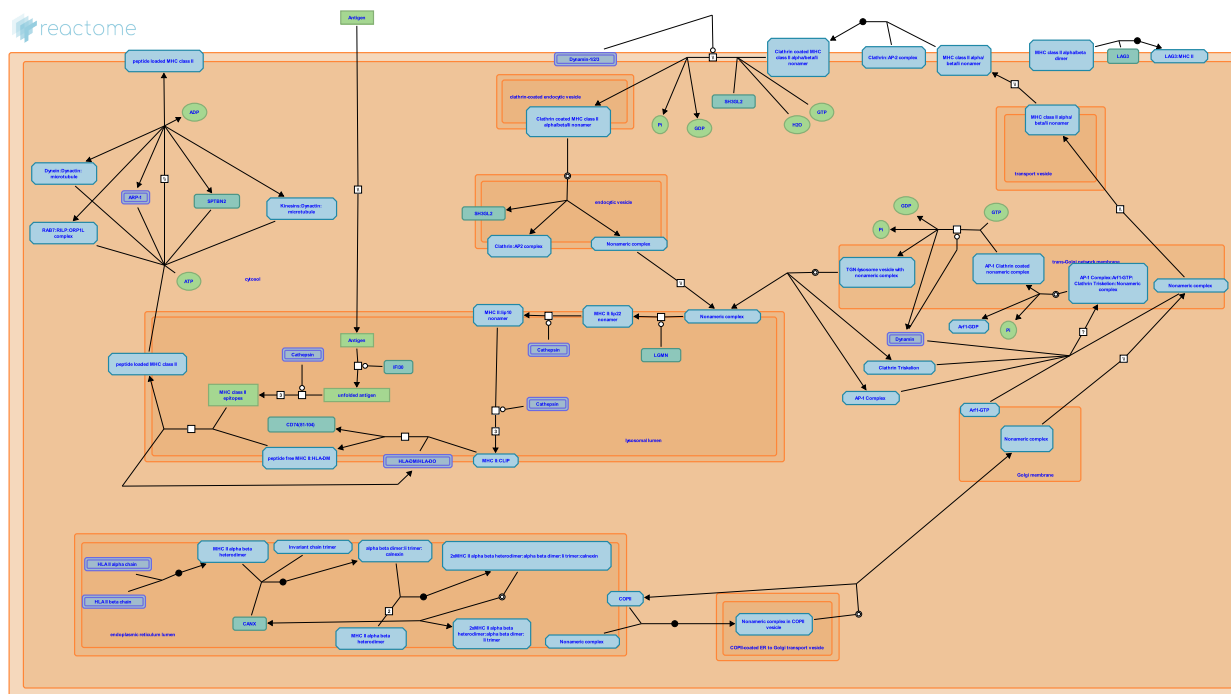


MHC class II antigen presentation



Garapati, P V., Jupe, S., Meldal, BH., Neefjes, J.

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](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/faq).

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](https://reactome.org/Textbook).

16/11/2024

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

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. [↗](#)

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)

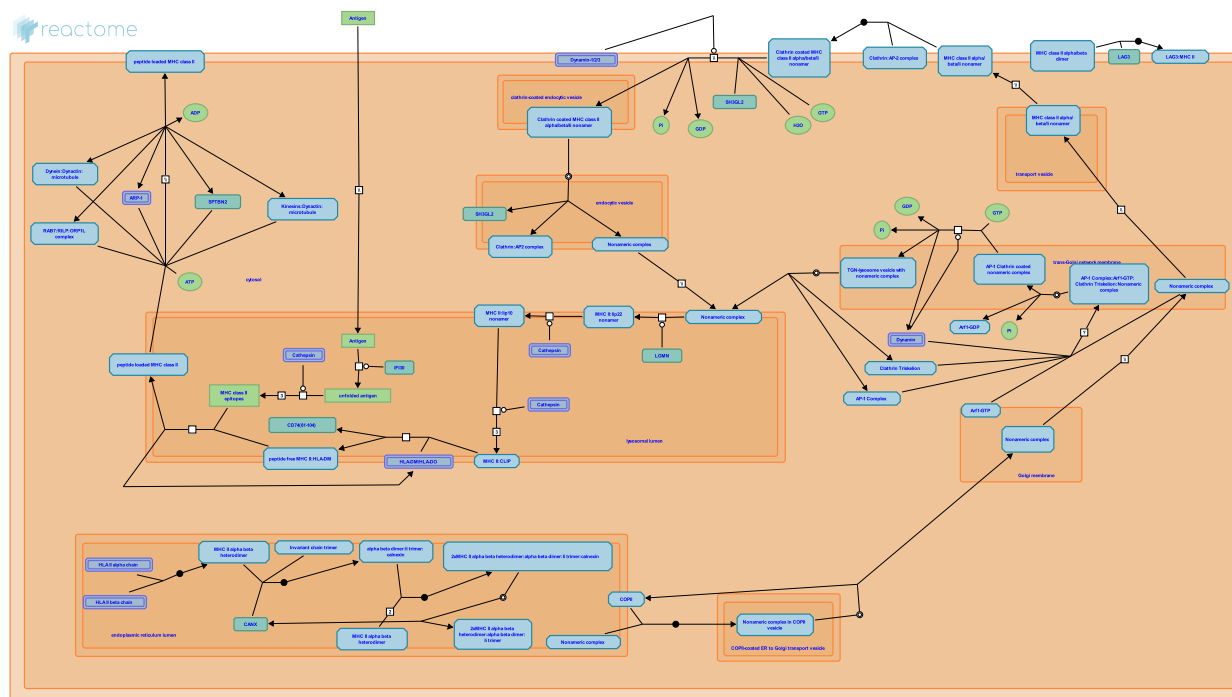
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 90

This document contains 1 pathway and 27 reactions ([see Table of Contents](#))

MHC class II antigen presentation ↗

Stable identifier: R-HSA-2132295



Antigen presenting cells (APCs) such as B cells, dendritic cells (DCs) and monocytes/macrophages express major histocompatibility complex class II molecules (MHC II) at their surface and present exogenous antigenic peptides to CD4⁺ T helper cells. CD4⁺ T cells play a central role in immune protection. On their activation they stimulate differentiation of B cells into antibody-producing B-cell blasts and initiate adaptive immune responses. MHC class II molecules are transmembrane glycoprotein heterodimers of alpha and beta subunits. Newly synthesized MHC II molecules present in the endoplasmic reticulum bind to a chaperone protein called invariant (Ii) chain. The binding of Ii prevents the premature binding of self antigens to the nascent MHC molecules in the ER and also guides MHC molecules to endocytic compartments. In the acidic endosomal environment, Ii is degraded in a stepwise manner, ultimately to free the class II peptide-binding groove for loading of antigenic peptides. Exogenous antigens are internalized by the APC by receptor mediated endocytosis, phagocytosis or pinocytosis into endocytic compartments of MHC class II positive cells, where engulfed antigens are degraded in a low pH environment by multiple acidic proteases, generating MHC class II epitopes. Antigenic peptides are then loaded into the class II ligand-binding groove. The resulting class II peptide complexes then move to the cell surface, where they are scanned by CD4⁺ T cells for specific recognition (Berger & Roche 2009, Zhou & Blum 2004, Watts 2004, Landsverk et al. 2009).

Literature references

- Ploegh, HL., Wolf, PR. (1995). How MHC class II molecules acquire peptide cargo: biosynthesis and trafficking through the endocytic pathway. *Annu Rev Cell Dev Biol*, 11, 267-306. ↗
- Jensen, PE. (1997). Peptide binding and antigen presentation by class II histocompatibility glycoproteins. *Biopolymers*, 43, 303-22. ↗
- Villadangos, JA. (2001). Presentation of antigens by MHC class II molecules: getting the most out of them. *Mol Immunol*, 38, 329-46. ↗
- Landsverk, OJ., Gregers, TF., Bakke, O. (2009). MHC II and the endocytic pathway: regulation by invariant chain. *Scand J Immunol*, 70, 184-93. ↗
- Simmons, D., Harding, CV., Ramachandra, L. (2009). MHC molecules and microbial antigen processing in phagosomes. *Curr Opin Immunol*, 21, 98-104. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

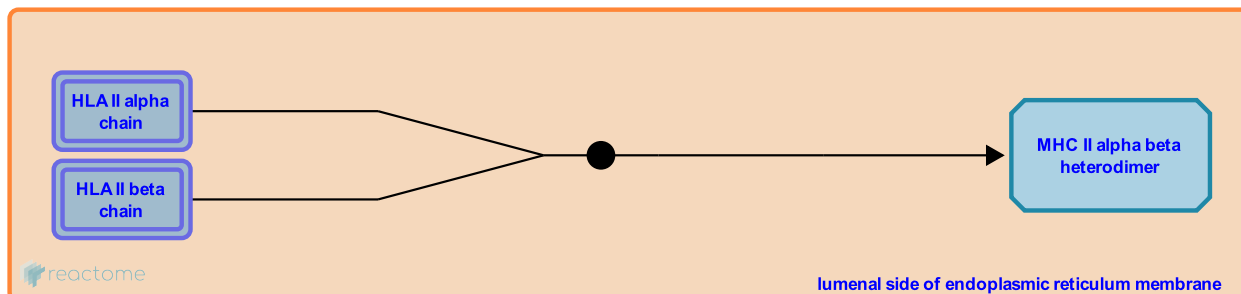
Formation of MHC II alpha beta heterodimer ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213239

Type: binding

Compartments: lumenal side of endoplasmic reticulum membrane



MHC II alpha and beta chains translocate to the ER and associate noncovalently to form an alpha beta heterodimer (Roche et al. 1991). This heterodimer then associates with a preformed invariant (Ii) chain trimer.

Followed by: [Interaction of invariant chain trimer and MHC II alpha beta dimer](#), [Formation of nonameric complex](#)

Literature references

- Neumann, J., Koch, N. (2005). Assembly of major histocompatibility complex class II subunits with invariant chain. *FEBS Lett*, 579, 6055-9. ↗
- Stumptner, P., Benaroch, P. (1997). Interaction of MHC class II molecules with the invariant chain: role of the invariant chain (81-90) region. *EMBO J*, 16, 5807-18. ↗
- Marks, MS., Roche, PA., Cresswell, P. (1991). Formation of a nine-subunit complex by HLA class II glycoproteins and the invariant chain. *Nature*, 354, 392-4. ↗
- Freisewinkel, IM., Schenck, K., Koch, N. (1993). The segment of invariant chain that is critical for association with major histocompatibility complex class II molecules contains the sequence of a peptide eluted from class II polypeptides. *Proc Natl Acad Sci U S A*, 90, 9703-6. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

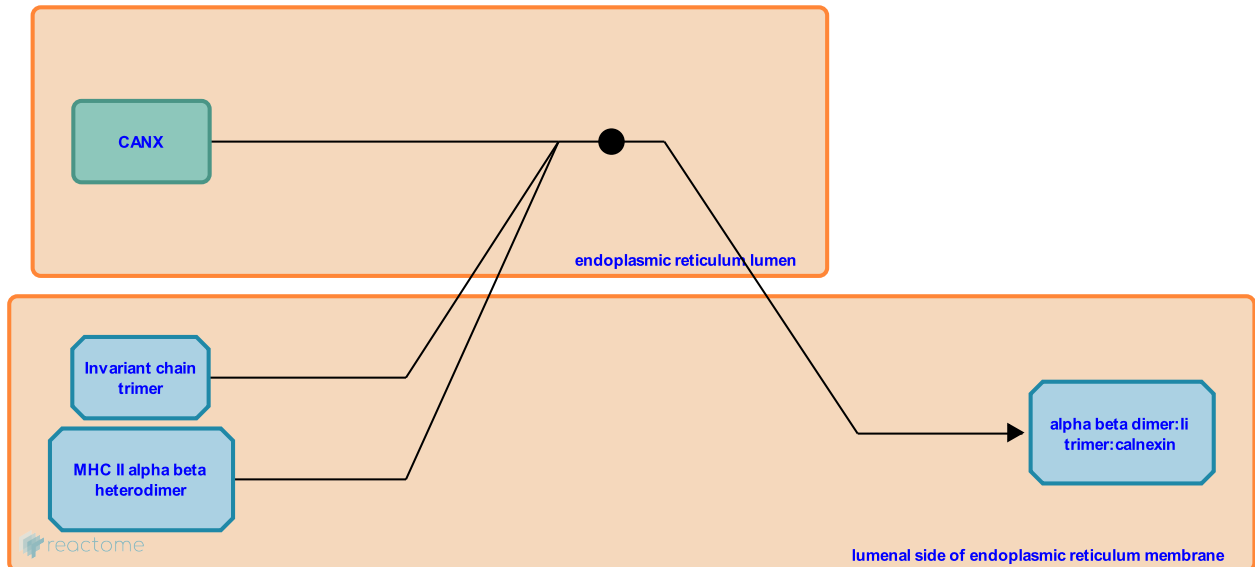
Interaction of invariant chain trimer and MHC II alpha beta dimer ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130478

Type: binding

Compartments: endoplasmic reticulum lumen, luminal side of endoplasmic reticulum membrane



MHC II alpha beta dimers associate with a third polypeptide, the invariant chain (Ii), required for class II molecules to reach the endocytic pathway (Roche et al. 1991). The interaction of Ii with the MHC II alpha beta dimer serves multiple functions. It plays a role in assembly, folding, egress from the ER and transport through the Golgi. Ii exists as a trimer; residues 163-183 of the Ii luminal domain are involved in covalent cross-linking. Residues 96-104 are critical for association with class II alpha beta dimers (Bijlmakers et al. 1994, Freisewinkel et al. 1993). Residues 89-104 known as CLIP (Class II-associated invariant chain peptide) are the part of the Ii chain that binds antigen binding MHC class II groove, remaining bound until the MHC receptor is completely assembled. This CLIP domain prevents the premature binding of self-peptide fragments present in ER prior to MHC II localization within the endosomal compartment. The ER-resident chaperone protein calnexin rapidly associates with newly synthesized alpha, beta and invariant chains, and remains associated until the final nonamer assembly. The stoichiometry of calnexin in this interaction and the dynamics of association-dissociation are not known. Calnexin may stabilize the free class II chains and regulate their intracellular transport by facilitating the production of transport competent molecules out of the ER (Anderson & Cresswell 1994, Schreiber et al. 1995).

Preceded by: [Formation of MHC II alpha beta heterodimer](#)

Followed by: [Formation of nonameric complex](#)

Literature references

- Cresswell, P., Anderson, KS. (1994). A role for calnexin (IP90) in the assembly of class II MHC molecules. *EMBO J*, 13, 675-82. ↗
- Rajagopalan, S., Huntoon, CJ., Bell, MP., Schreiber, KL., Brenner, MB., McKean, DJ. (1994). Class II histocompatibility molecules associate with calnexin during assembly in the endoplasmic reticulum. *Int Immunol*, 6, 101-11. ↗
- Roche, PA., Cresswell, P. (1990). Invariant chain association with HLA-DR molecules inhibits immunogenic peptide binding. *Nature*, 345, 615-8. ↗
- Barois, N., Landsverk, OJ., Gregers, TF., Bakke, O. (2011). Invariant chain increases the half-life of MHC II by delaying endosomal maturation. *Immunol Cell Biol*, 89, 619-29. ↗
- Stumptner, P., Benaroch, P. (1997). Interaction of MHC class II molecules with the invariant chain: role of the invariant chain (81-90) region. *EMBO J*, 16, 5807-18. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

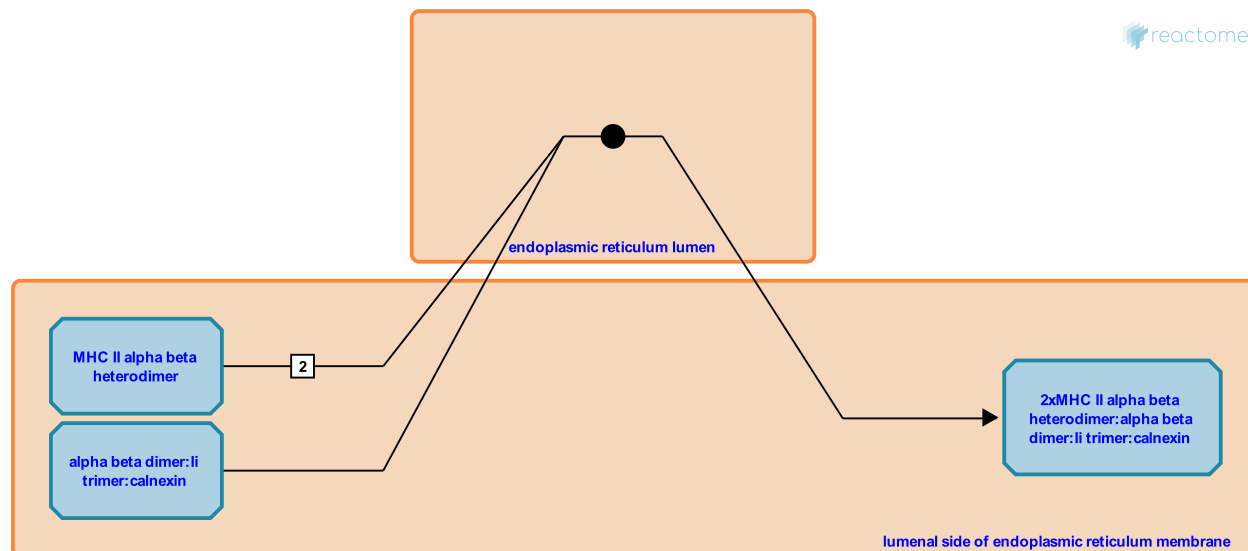
Formation of nonameric complex ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213241

Type: binding

Compartments: endoplasmic reticulum lumen, luminal side of endoplasmic reticulum membrane



Progressive addition of two more preformed alpha beta dimers to the invariant chain trimer and alpha beta complex ((alpha beta)₁:Ii)₃ forms the complete nonameric structure ((alpha beta:Ii)₃). Calnexin then disassociates on egress of the nonameric complex from the ER.

Preceded by: [Interaction of invariant chain trimer and MHC II alpha beta dimer](#), [Formation of MHC II alpha beta heterodimer](#)

Followed by: [Dissociation of CANX from nonameric complex](#)

Literature references

Stumptner, P., Benaroch, P. (1997). Interaction of MHC class II molecules with the invariant chain: role of the invariant chain (81-90) region. *EMBO J*, 16, 5807-18. ↗

Marks, MS., Roche, PA., Cresswell, P. (1991). Formation of a nine-subunit complex by HLA class II glycoproteins and the invariant chain. *Nature*, 354, 392-4. ↗

Dixon, AM., Matthews, EE., Stanley, BJ., Engelman, DM., Dawson, JP. (2006). Invariant chain transmembrane domain trimerization: a step in MHC class II assembly. *Biochemistry*, 45, 5228-34. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

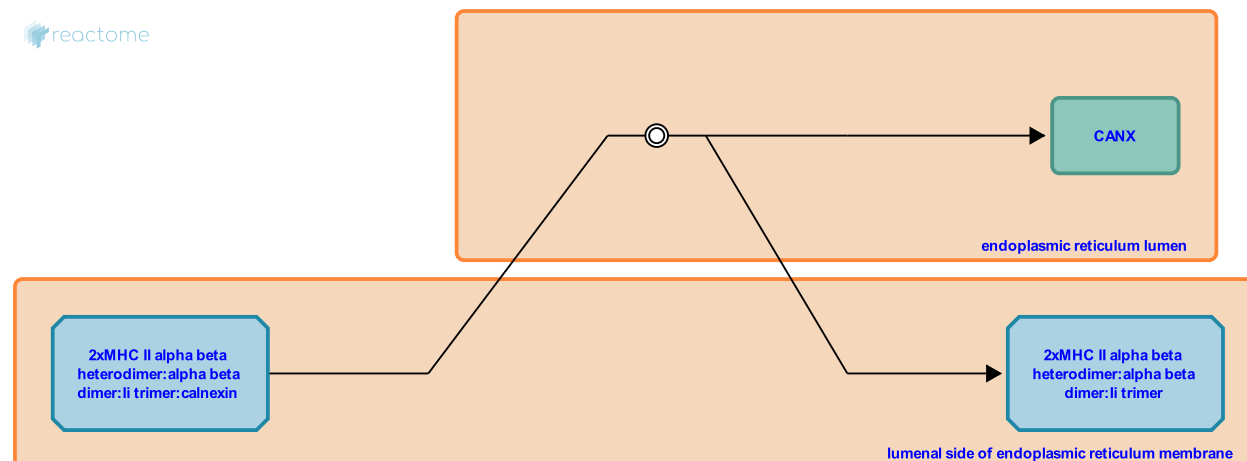
Dissociation of CANX from nonameric complex ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-8951500

Type: dissociation

Compartments: endoplasmic reticulum lumen, luminal side of endoplasmic reticulum membrane



Calnexin disassociates on egress of the nonameric complex from the ER.

Preceded by: [Formation of nonameric complex](#)

Followed by: [Formation of COPII vesicle](#)

Literature references

Stumptner, P., Benaroch, P. (1997). Interaction of MHC class II molecules with the invariant chain: role of the invariant chain (81-90) region. *EMBO J*, 16, 5807-18. ↗

Marks, MS., Roche, PA., Cresswell, P. (1991). Formation of a nine-subunit complex by HLA class II glycoproteins and the invariant chain. *Nature*, 354, 392-4. ↗

Dixon, AM., Matthews, EE., Stanley, BJ., Engelman, DM., Dawson, JP. (2006). Invariant chain transmembrane domain trimerization: a step in MHC class II assembly. *Biochemistry*, 45, 5228-34. ↗

Editions

2012-02-21	Authored	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.
2016-12-09	Edited	Jupe, S.

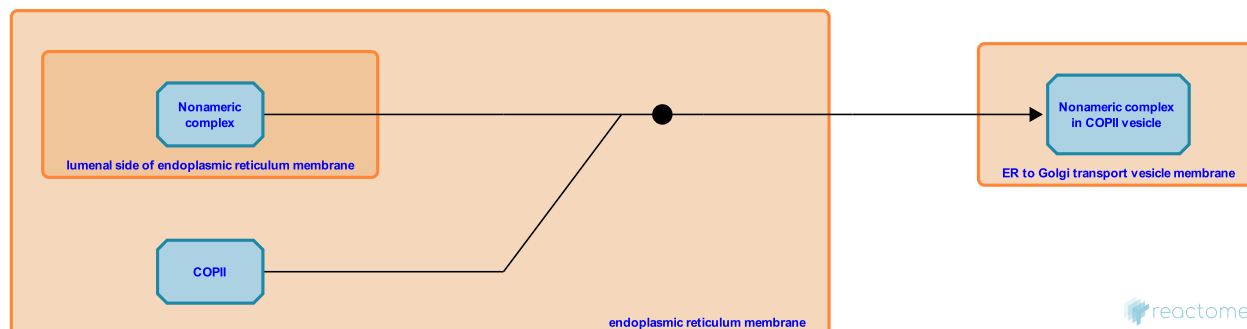
Formation of COPII vesicle ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130731

Type: binding

Compartments: endoplasmic reticulum membrane, COPII-coated ER to Golgi transport vesicle, luminal side of endoplasmic reticulum membrane



Immediately after assembly in the ER nonameric ($\alpha\beta\gamma\text{Ii}$)₃ complexes egress from ER, facilitated by the presence of Ii, and enter the Golgi complex (Wolf & Ploegh 1995, Geuze 1998). Incorrectly folded or oligomerized α , β and Ii chains are retained in the ER and degraded. The Sec23/24-Sar1 pre-budding complex binds to the nonameric complex and then recruits Sec13/31 outer shell, which buds off from the membrane as a coat protein complex II (COPII) vesicle to be transported to the Golgi complex (Bickford et al. 2004).

Preceded by: [Dissociation of CANX from nonameric complex](#)

Followed by: [Transport of MHC II:Ii complex along Golgi to TGN](#), [Fusion of COPII vesicle with Golgi complex](#)

Literature references

Roche, PA., Hiltbold, EM. (2002). Trafficking of MHC class II molecules in the late secretory pathway. *Curr Opin Immunol*, 14, 30-5. ↗

Marks, MS., Blum, JS., Cresswell, P. (1990). Invariant chain trimers are sequestered in the rough endoplasmic reticulum in the absence of association with HLA class II antigens. *J Cell Biol*, 111, 839-55. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

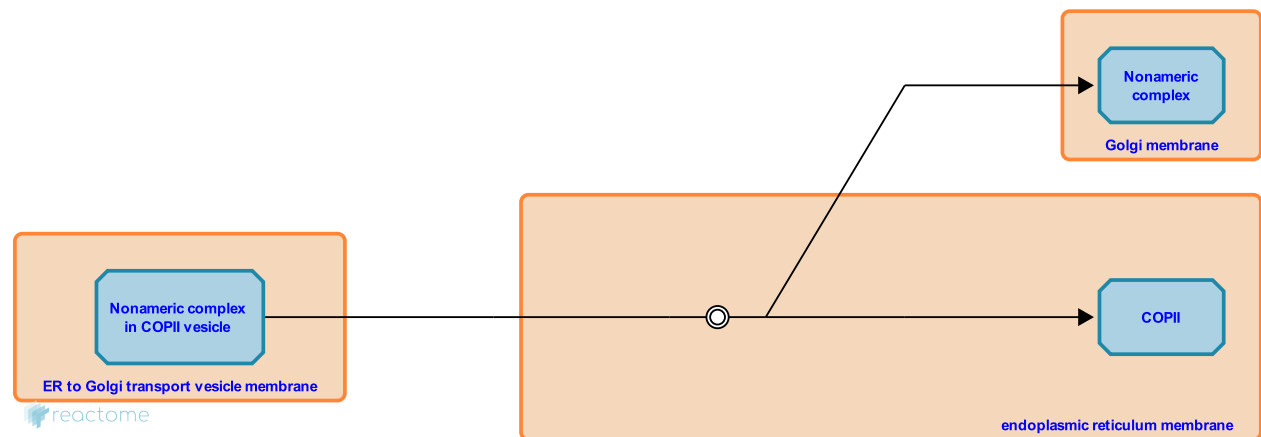
Fusion of COPII vesicle with Golgi complex ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213243

Type: dissociation

Compartments: endoplasmic reticulum membrane, Golgi membrane, ER to Golgi transport vesicle membrane



The COPII vesicle uncoats and fuses with the cis-Golgi, releasing the MHC II:Ii complex into the Golgi.

Preceded by: [Formation of COPII vesicle](#)

Followed by: [Transport of MHC II:Ii complex along Golgi to TGN](#)

Literature references

Roche, PA., Hiltbold, EM. (2002). Trafficking of MHC class II molecules in the late secretory pathway. *Curr Opin Immunol*, 14, 30-5. ↗

Davidson, HW. (1999). Direct transport of newly synthesized HLA-DR from the trans-Golgi network to major histocompatibility complex class II containing compartments (MIICS) demonstrated using a novel tyrosine-sulfated chimera. *J Biol Chem*, 274, 27315-22. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

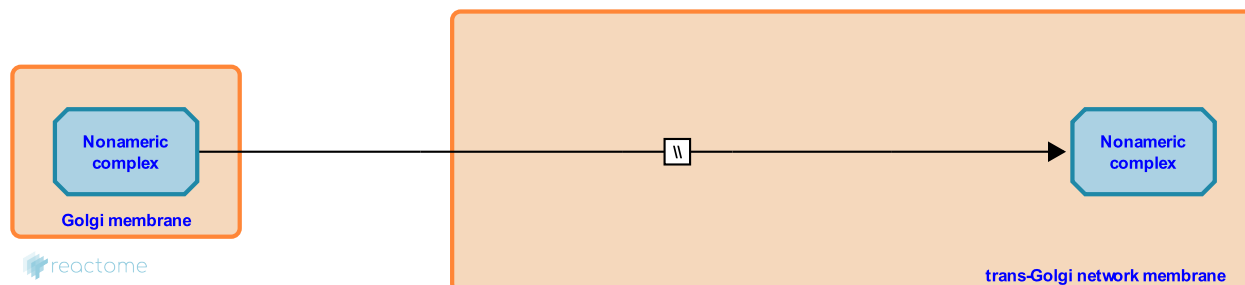
Transport of MHC II:Ii complex along Golgi to TGN ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130393

Type: omitted

Compartments: trans-Golgi network membrane, Golgi membrane



Nonameric MHC II:Ii complex move through the various cisternae to reach the trans-golgi network (TGN), a tubulo-vesicular organelle located at the trans-face of Golgi stacks. From the TGN, MHC II:Ii complexes are targeted to the endocytic pathway for peptide loading.

Preceded by: [Formation of COPII vesicle](#), [Fusion of COPII vesicle with Golgi complex](#)

Followed by: [TGN-lysosomal vesicle coat assembly](#), [Transport of MHC II:Ii complex to plasma membrane](#)

Literature references

- Roche, PA., Hiltbold, EM. (2002). Trafficking of MHC class II molecules in the late secretory pathway. *Curr Opin Immunol*, 14, 30-5. ↗
- Crump, CM., Gu, F., Thomas, G. (2001). Trans-Golgi network sorting. *Cell Mol Life Sci*, 58, 1067-84. ↗
- Davidson, HW. (1999). Direct transport of newly synthesized HLA-DR from the trans-Golgi network to major histocompatibility complex class II containing compartments (MIICS) demonstrated using a novel tyrosine-sulfated chimera. *J Biol Chem*, 274, 27315-22. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

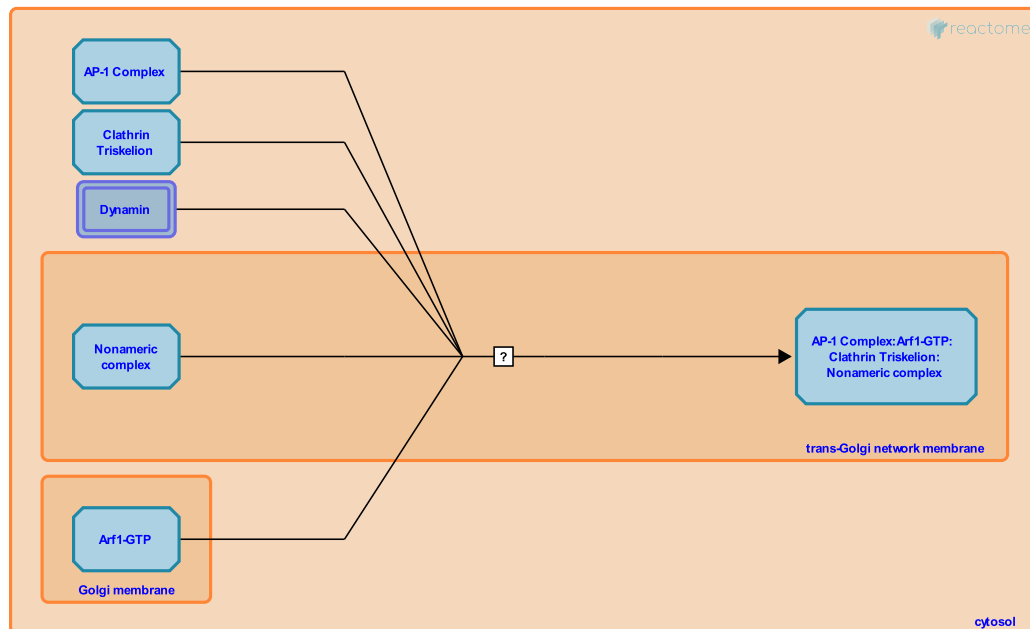
TGN-lysosomal vesicle coat assembly ↗

Location: MHC class II antigen presentation

Stable identifier: R-HSA-2130619

Type: uncertain

Compartments: trans-Golgi network membrane, Golgi membrane, cytosol



The trans-Golgi network (TGN) is the sorting and package centre for trafficking cargo to the endoplasmic reticulum, plasma membrane and endosomes. Signal peptides determine the sorting and trafficking of proteins to the endosomal-lysosomal pathway or to the cell surface. The main signals that mediate targeting of MHC-II molecules to the endocytic pathway are two dileucine-based motifs, Leu23-Ile24 and Pro31-Leu33 present in the short cytoplasmic tail of Ii (Odorizzi et al. 1994). These motifs bind both the adaptor proteins AP-1 and AP-2, which are components of clathrin coats associated with the TGN/endosomes and the plasma membrane, respectively (McCormick et al. 2005). The precise pathway of class II:Ii complex trafficking from TGN to endocytic pathway is not well understood. In one view MHC II:Ii complexes directly traffic from the TGN to lysosomes, possibly using AP-1 dependent endocytic vesicles (Peters et al. 1991, Amigorena et al. 1994). Alternatively trafficking occurs via transient expression on the cell surface followed by rapid internalization and delivery to endocytic compartments. Early immunoelectron microscopy data has shown the presence of MHC class II:Ii complex molecules primarily in TGN and lysosomes (Peters et al. 1991, Hiltbold & Roche 2002). This theory was further supported by a study examining the trafficking of sulphate-tagged class II molecules, which concluded that the rapid appearance of these molecules in lysosomes was consistent with their direct transport from the TGN to lysosomes (Hiltbold & Roche 2002, Davidson 1999). The transport of cargo MHC II:Ii complexes from the TGN to lysosomes may be mediated by small TGN vesicles coated with AP-1 and clathrin. The di-leucine-based sorting signal in the Ii cytoplasmic chain recruits AP-1 and clathrin from cytosol to TGN to form AP-1 clathrin-coated TGN-derived vesicles. This process is regulated by the small GTPase ARF-1 (Salamero et al. 1996).

Preceded by: Transport of MHC II:Ii complex along Golgi to TGN

Followed by: Dissociation of Arf1:GDP, AP-1 Clathrin coated nonameric complex, Translocation of TGN-lysosome vesicle to lysosome

Literature references

- Peterson, PA., Tainer, JA., Pond, L., Schutze, MP., Jackson, MR., Teyton, L. et al. (1995). A role for acidic residues in di-leucine motif-based targeting to the endocytic pathway. *J Biol Chem*, 270, 19989-97. ↗
- Davidson, HW. (1999). Direct transport of newly synthesized HLA-DR from the trans-Golgi network to major histocompatibility complex class II containing compartments (MIICS) demonstrated using a novel tyrosine-sulfated chimera. *J Biol Chem*, 274, 27315-22. ↗

Goud, B., Hoflack, B., Salamero, J., Le Borgne, R., Saudrais, C. (1996). Expression of major histocompatibility complex class II molecules in HeLa cells promotes the recruitment of AP-1 Golgi-specific assembly proteins on Golgi membranes. *J Biol Chem*, 271, 30318-21. [↗](#)

Morelli, MA., Frank, RW., Saviano, G., Bremnes, B., Motta, A., Bakke, O. (1995). Structure-activity relationship of the leucine-based sorting motifs in the cytosolic tail of the major histocompatibility complex-associated invariant chain. *J Biol Chem*, 270, 27165-71. [↗](#)

Rodionov, DG., Bakke, O. (1998). Medium chains of adaptor complexes AP-1 and AP-2 recognize leucine-based sorting signals from the invariant chain. *J Biol Chem*, 273, 6005-8. [↗](#)

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

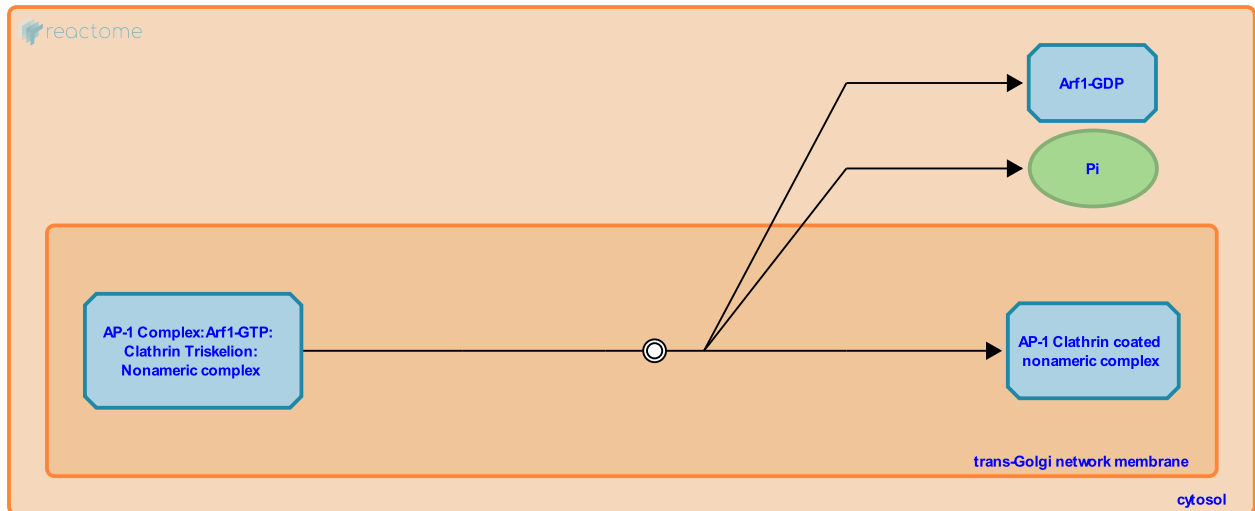
Dissociation of Arf1:GDP, AP-1 Clathrin coated nonameric complex ↗

Location: MHC class II antigen presentation

Stable identifier: R-HSA-8951498

Type: dissociation

Compartments: trans-Golgi network membrane, Golgi membrane, cytosol



The trans-Golgi network (TGN) is the sorting and package centre for trafficking cargo to the endoplasmic reticulum, plasma membrane and endosomes. Signal peptides determine the sorting and trafficking of proteins to the endosomal-lysosomal pathway or to the cell surface. The main signals that mediate targeting of MHC-II molecules to the endocytic pathway are two dileucine-based motifs, Leu23-Ile24 and Pro31-Leu33 present in the short cytoplasmic tail of Ii (Odorizzi et al. 1994). These motifs bind both the adaptor proteins AP-1 and AP-2, which are components of clathrin coats associated with the TGN/endosomes and the plasma membrane, respectively (McCormick et al. 2005). The precise pathway of class II:Ii complex trafficking from TGN to endocytic pathway is not well understood. In one view MHC II:Ii complexes directly traffic from the TGN to lysosomes, possibly using AP-1 dependent endocytic vesicles (Peters et al. 1991, Amigorena et al. 1994). Alternatively trafficking occurs via transient expression on the cell surface followed by rapid internalization and delivery to endocytic compartments. Early immunoelectron microscopy data has shown the presence of MHC class II:Ii complex molecules primarily in TGN and lysosomes (Peters et al. 1991, Hiltbold & Roche 2002). This theory was further supported by a study examining the trafficking of sulphate-tagged class II molecules, which concluded that the rapid appearance of these molecules in lysosomes was consistent with their direct transport from the TGN to lysosomes (Hiltbold & Roche 2002, Davidson 1999). The transport of cargo MHC II:Ii complexes from the TGN to lysosomes may be mediated by small TGN vesicles coated with AP-1 and clathrin. The di-leucine-based sorting signal in the Ii cytoplasmic chain recruits AP-1 and clathrin from cytosol to TGN to form AP-1 clathrin-coated TGN-derived vesicles. This process is regulated by the small GTPase ARF-1 (Salamero et al. 1996).

Preceded by: TGN-lysosomal vesicle coat assembly

Literature references

- Peterson, PA., Tainer, JA., Pond, L., Schutze, MP., Jackson, MR., Teyton, L. et al. (1995). A role for acidic residues in di-leucine motif-based targeting to the endocytic pathway. *J Biol Chem*, 270, 19989-97. ↗
- Davidson, HW. (1999). Direct transport of newly synthesized HLA-DR from the trans-Golgi network to major histocompatibility complex class II containing compartments (MIICS) demonstrated using a novel tyrosine-sulfated chimera. *J Biol Chem*, 274, 27315-22. ↗
- Goud, B., Hoflack, B., Salamero, J., Le Borgne, R., Saudrais, C. (1996). Expression of major histocompatibility complex class II molecules in HeLa cells promotes the recruitment of AP-1 Golgi-specific assembly proteins on Golgi membranes. *J Biol Chem*, 271, 30318-21. ↗
- Morelli, MA., Frank, RW., Saviano, G., Bremnes, B., Motta, A., Bakke, O. (1995). Structure-activity relationship of the leucine-based sorting motifs in the cytosolic tail of the major histocompatibility complex-associated invariant chain. *J Biol Chem*, 270, 27165-71. ↗

Rodionov, DG., Bakke, O. (1998). Medium chains of adaptor complexes AP-1 and AP-2 recognize leucine-based sorting signals from the invariant chain. *J Biol Chem*, 273, 6005-8. [↗](#)

Editions

2012-02-21	Authored	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.
2016-12-09	Edited	Jupe, S.

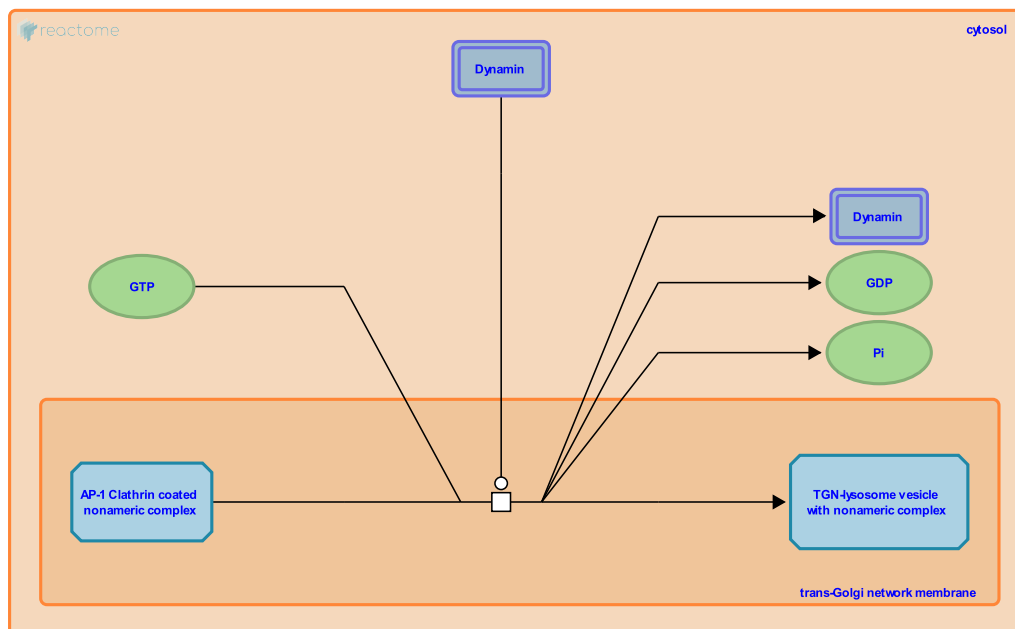
Translocation of TGN-lysosome vesicle to lysosome ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130641

Type: transition

Compartments: trans-Golgi network membrane, cytosol



Budding vesicles loaded with the nonameric complex bud off from the TGN to reach the late-endosome/lysosome membrane.

Preceded by: [TGN-lysosomal vesicle coat assembly](#)

Followed by: [TGN-lysosome vesicle uncoating and release of nonameric complex to lysosome](#)

Literature references

- Peterson, PA., Tainer, JA., Pond, L., Schutze, MP., Jackson, MR., Teyton, L. et al. (1995). A role for acidic residues in di-leucine motif-based targeting to the endocytic pathway. *J Biol Chem*, 270, 19989-97. ↗
- Davidson, HW. (1999). Direct transport of newly synthesized HLA-DR from the trans-Golgi network to major histocompatibility complex class II containing compartments (MIICS) demonstrated using a novel tyrosine-sulfated chimera. *J Biol Chem*, 274, 27315-22. ↗
- Goud, B., Hoflack, B., Salamero, J., Le Borgne, R., Saudrais, C. (1996). Expression of major histocompatibility complex class II molecules in HeLa cells promotes the recruitment of AP-1 Golgi-specific assembly proteins on Golgi membranes. *J Biol Chem*, 271, 30318-21. ↗
- Morelli, MA., Frank, RW., Saviano, G., Bremnes, B., Motta, A., Bakke, O. (1995). Structure-activity relationship of the leucine-based sorting motifs in the cytosolic tail of the major histocompatibility complex-associated invariant chain. *J Biol Chem*, 270, 27165-71. ↗
- Rodionov, DG., Bakke, O. (1998). Medium chains of adaptor complexes AP-1 and AP-2 recognize leucine-based sorting signals from the invariant chain. *J Biol Chem*, 273, 6005-8. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

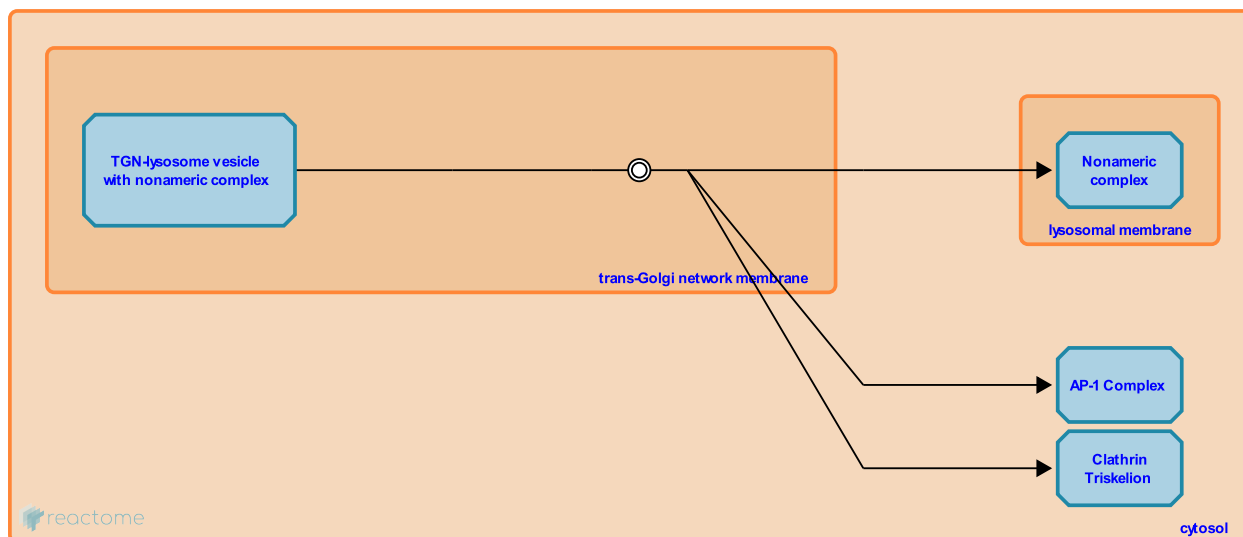
TGN-lysosome vesicle uncoating and release of nonameric complex to lysosome ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213236

Type: dissociation

Compartments: trans-Golgi network membrane, cytosol, lysosomal membrane



On reaching the late endosomes/lysosomes the TGN-lysosome vesicle uncoats and fuses with the lysosome to releases the MHC II nonameric complex.

Preceded by: [Translocation of TGN-lysosome vesicle to lysosome](#)

Followed by: [Initial proteolysis of Ii by aspartic proteases to lip22](#)

Literature references

Peterson, PA., Tainer, JA., Pond, L., Schutze, MP., Jackson, MR., Teyton, L. et al. (1995). A role for acidic residues in di-leucine motif-based targeting to the endocytic pathway. *J Biol Chem*, 270, 19989-97. ↗

Davidson, HW. (1999). Direct transport of newly synthesized HLA-DR from the trans-Golgi network to major histocompatibility complex class II containing compartments (MIICS) demonstrated using a novel tyrosine-sulfated chimera. *J Biol Chem*, 274, 27315-22. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

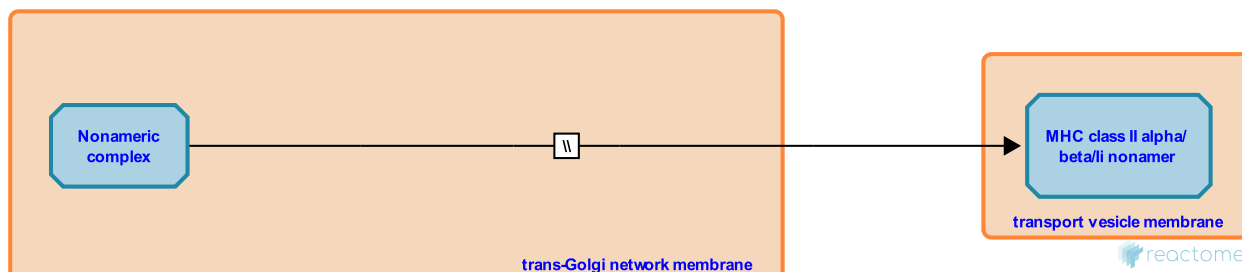
Transport of MHC II:Ii complex to plasma membrane ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130378

Type: omitted

Compartments: trans-Golgi network membrane, transport vesicle membrane



The newly formed MHC II-Ii complex exits the TGN and ultimately is delivered to late-endosome/lysosome compartments. A proportion of the nonameric complex traffics directly from the TGN to these compartments, while a substantial population follow the indirect pathway involving transport from the TGN to the plasma membrane, followed by endocytic delivery to early endosomes, late endosomes, and finally lysosomes (McCormick et al. 2005). Transport carrier vesicles may traffic the cargo MHC II-Ii complex from the TGN to the plasma membrane.

Preceded by: [Transport of MHC II:Ii complex along Golgi to TGN](#)

Followed by: [Insertion of MHC II:Ii complex in to the plasma membrane](#)

Literature references

- Teletski, CL., Roche, PA., Long, EO., Stang, E., Bakke, O. (1993). Cell surface HLA-DR-invariant chain complexes are targeted to endosomes by rapid internalization. *Proc Natl Acad Sci U S A*, 90, 8581-5. ↗
- Mattes, MJ., Goldenberg, DM., Hansen, HJ., Ong, GL. (1999). Cell surface expression and metabolism of major histocompatibility complex class II invariant chain (CD74) by diverse cell lines. *Immunology*, 98, 296-302. ↗
- Malhotra, V., Bard, F. (2006). The formation of TGN-to-plasma-membrane transport carriers. *Annu Rev Cell Dev Biol*, 22, 439-55. ↗
- Sandoval, IV., Bakke, O. (1994). Targeting of membrane proteins to endosomes and lysosomes. *Trends Cell Biol*, 4, 292-7. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

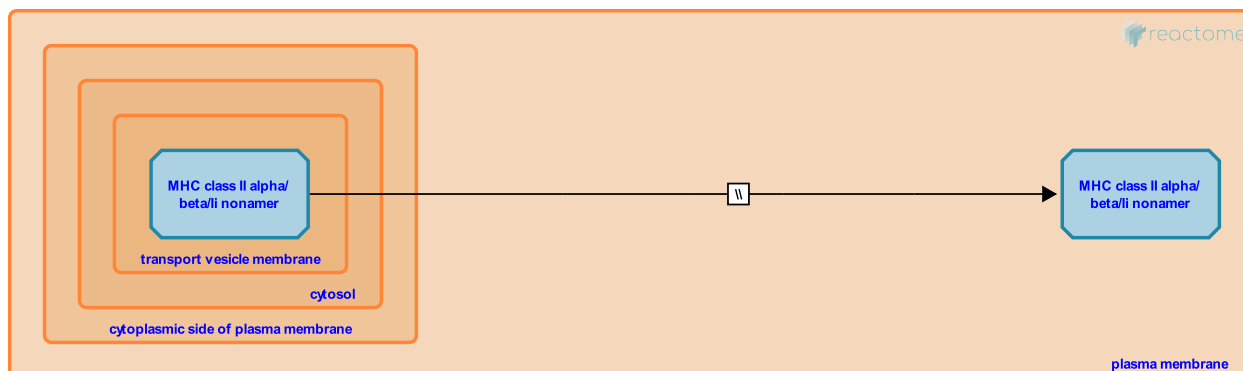
Insertion of MHC II:Ii complex in to the plasma membrane ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130500

Type: omitted

Compartments: plasma membrane, transport vesicle membrane



On reaching the cell surface, transport carrier vesicles insert the cargo MHC II:Ii complex into the plasma membrane.

Preceded by: [Transport of MHC II:Ii complex to plasma membrane](#)

Followed by: [Recruitment of clathrin coated vesicle by Ii](#)

Literature references

Teletski, CL., Roche, PA., Long, EO., Stang, E., Bakke, O. (1993). Cell surface HLA-DR-invariant chain complexes are targeted to endosomes by rapid internalization. *Proc Natl Acad Sci U S A*, 90, 8581-5. ↗

Mattes, MJ., Goldenberg, DM., Hansen, HJ., Ong, GL. (1999). Cell surface expression and metabolism of major histocompatibility complex class II invariant chain (CD74) by diverse cell lines. *Immunology*, 98, 296-302. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

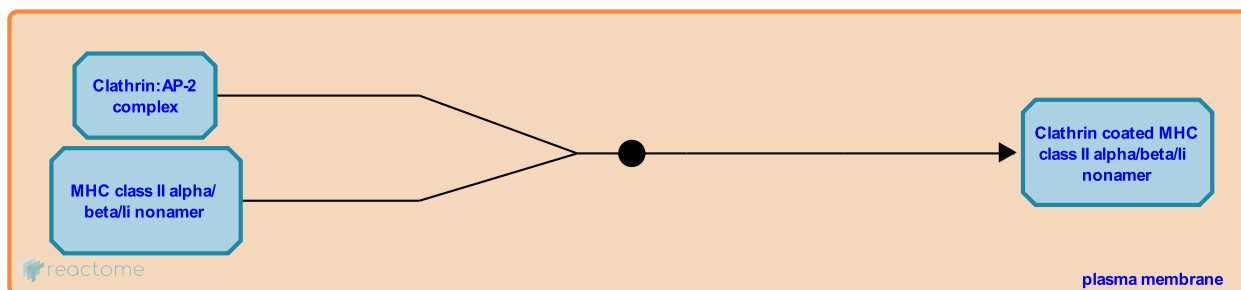
Recruitment of clathrin coated vesicle by Ii ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130640

Type: binding

Compartments: plasma membrane



Plasma membrane-associated nonameric complexes (MHC II alpha/beta/Ii complex) are rapidly internalized and delivered to late endosomes (LEs) and lysosomes. The dileucine-based signal present in the cytoplasmic tail of Ii is required for sorting of the nonameric MHC II-Ii complex from the plasma membrane to peptide loading compartments. These signals promote rapid internalization by recognising and binding to clathrin adaptor AP-2, a scaffolding-protein complex that brings together components of the vesicle-formation machinery. AP-2 is an essential component of an endocytic clathrin coat and participates in initiation of coat assembly. The critical role of AP2 in delivering MHC II:Ii complex to antigen processing compartments came from RNA interference studies targeting clathrin and AP2. The knockout of AP2 profoundly inhibited MHC II:Ii complex internalization and resulted in the accumulation of Ii at the surface (Dugast et al. 2005, McCormick et al. 2005).

Preceded by: [Insertion of MHC II:Ii complex in to the plasma membrane](#)

Followed by: [Internalization of MHC II:Ii clathrin coated vesicle](#)

Literature references

- Dousset, C., Toussaint, H., Benaroch, P., Dugast, M. (2005). AP2 clathrin adaptor complex, but not AP1, controls the access of the major histocompatibility complex (MHC) class II to endosomes. *J Biol Chem*, 280, 19656-64. ↗
- Teletski, CL., Roche, PA., Long, EO., Stang, E., Bakke, O. (1993). Cell surface HLA-DR-invariant chain complexes are targeted to endosomes by rapid internalization. *Proc Natl Acad Sci U S A*, 90, 8581-5. ↗
- Martina, JA., McCormick, PJ., Bonifacino, JS. (2005). Involvement of clathrin and AP-2 in the trafficking of MHC class II molecules to antigen-processing compartments. *Proc Natl Acad Sci U S A*, 102, 7910-5. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

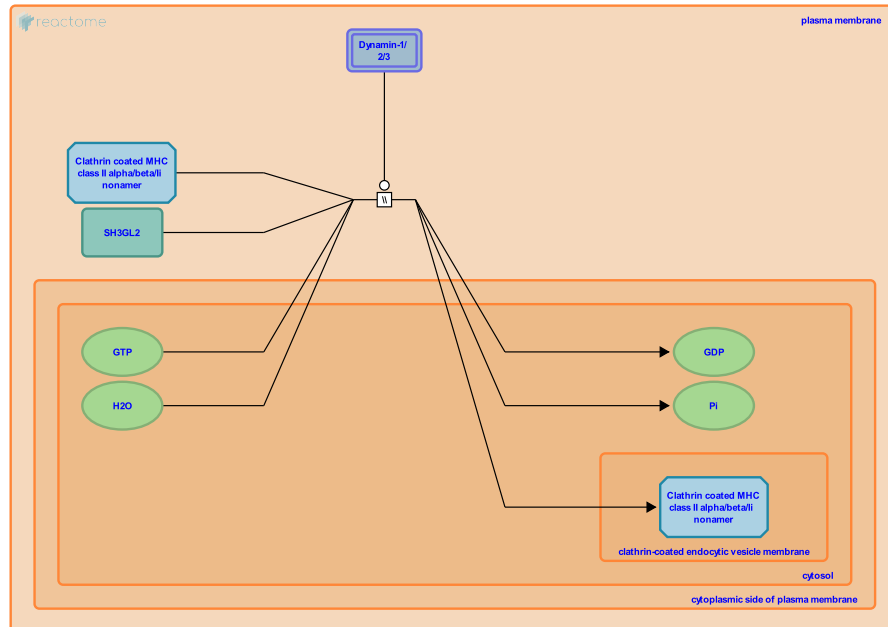
Internalization of MHC II:Ii clathrin coated vesicle ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130725

Type: omitted

Compartments: plasma membrane, cytosol, clathrin-coated endocytic vesicle membrane



MHC II:Ii complexes are internalized into the endocytic clathrin-coated-pit. Dynamin, the GTPase involved in the scission of clathrin-coated vesicles from plasma membrane, is observed to be involved in the effective endocytosis of MHC II:Ii complexes. Wang et al. demonstrated that overexpression of a dominant-negative mutant of the GTPase dynamin resulted in the cell surface accumulation of MHC II:Ii complex, supporting that endocytosis is required for delivery to antigen processing compartments (Wang et al., 1997). However, another study using the same dynamin mutant generated opposite conclusions (Davidson, 1999). This discrepancy may be caused by differences in experimental set-up and in the levels of expression of the dynamin mutant and MHC II chains (Dugast et al., 2005).

Preceded by: [Recruitment of clathrin coated vesicle by Ii](#)

Followed by: [Uncoating of clathrin-coated vesicles and fusion with endosomes](#)

Literature references

- Dousset, C., Toussaint, H., Benaroch, P., Dugast, M. (2005). AP2 clathrin adaptor complex, but not AP1, controls the access of the major histocompatibility complex (MHC) class II to endosomes. *J Biol Chem*, 280, 19656-64. ↗
- Teletski, CL., Roche, PA., Long, EO., Stang, E., Bakke, O. (1993). Cell surface HLA-DR-invariant chain complexes are targeted to endosomes by rapid internalization. *Proc Natl Acad Sci U S A*, 90, 8581-5. ↗
- Davidson, HW. (1999). Direct transport of newly synthesized HLA-DR from the trans-Golgi network to major histocompatibility complex class II containing compartments (MIICS) demonstrated using a novel tyrosine-sulfated chimera. *J Biol Chem*, 274, 27315-22. ↗
- Peterson, PA., Karlsson, L., Wang, K. (1997). Decreased endosomal delivery of major histocompatibility complex class II-invariant chain complexes in dynamin-deficient cells. *J Biol Chem*, 272, 17055-60. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

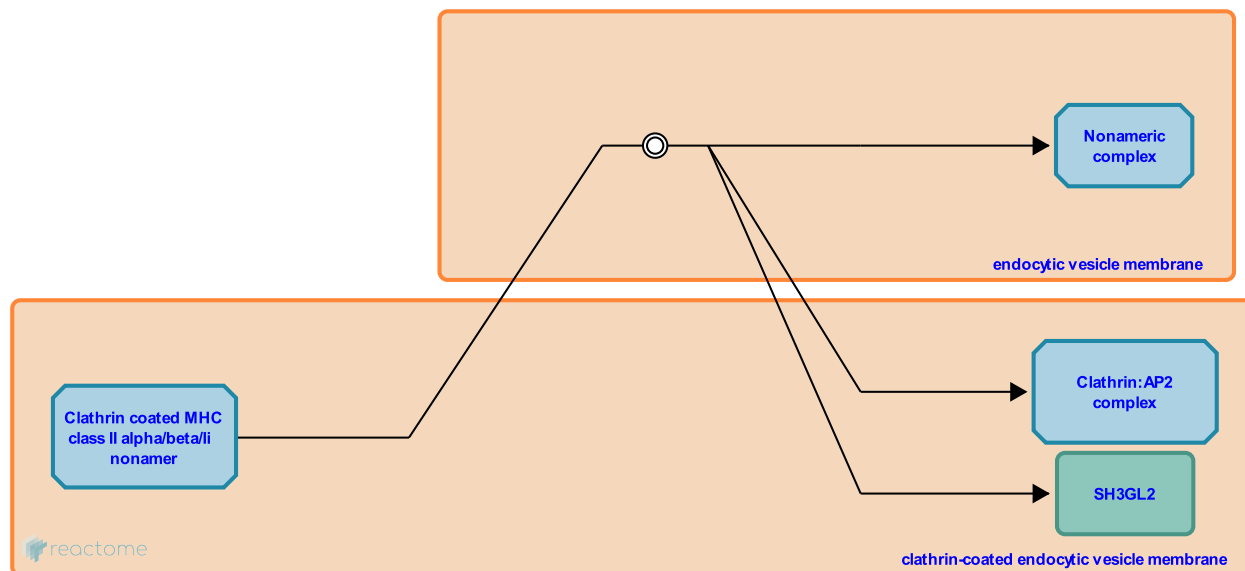
Uncoating of clathrin-coated vesicles and fusion with endosomes ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130486

Type: dissociation

Compartments: endocytic vesicle membrane, clathrin-coated endocytic vesicle



MHC II:II complexes bound to clathrin-coated vesicles rapidly fuse with endosomes.

Preceded by: [Internalization of MHC II:II clathrin coated vesicle](#)

Followed by: [Trafficking of nonameric complex in the endocytic pathway](#)

Literature references

Teletski, CL., Roche, PA., Long, EO., Stang, E., Bakke, O. (1993). Cell surface HLA-DR-invariant chain complexes are targeted to endosomes by rapid internalization. *Proc Natl Acad Sci U S A*, 90, 8581-5. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

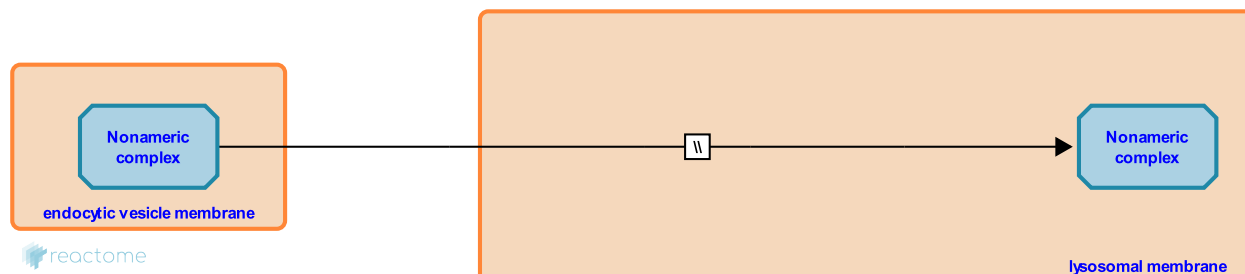
Trafficking of nonameric complex in the endocytic pathway ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213235

Type: omitted

Compartments: lysosomal membrane, endocytic vesicle membrane



The internalized nonameric complex passes through the endocytic pathway and finally reach the acidic late endosomal/lysosomal compartments, where the Ii component is progressively degraded by proteases. Proteolysis of Ii occurs through sequential cleavages from the luminal (C-terminal) side, generating cleavage products of approximately 22 kDa (lip22) and 10 kDa (lip10), finally leaving only CLIP bound within the peptide binding groove of MHC II (Landsverk et al. 2009).

Preceded by: [Uncoating of clathrin-coated vesicles and fusion with endosomes](#)

Followed by: [Initial proteolysis of Ii by aspartic proteases to lip22](#)

Literature references

Sandoval, IV., Bakke, O. (1994). Targeting of membrane proteins to endosomes and lysosomes. *Trends Cell Biol*, 4, 292-7. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

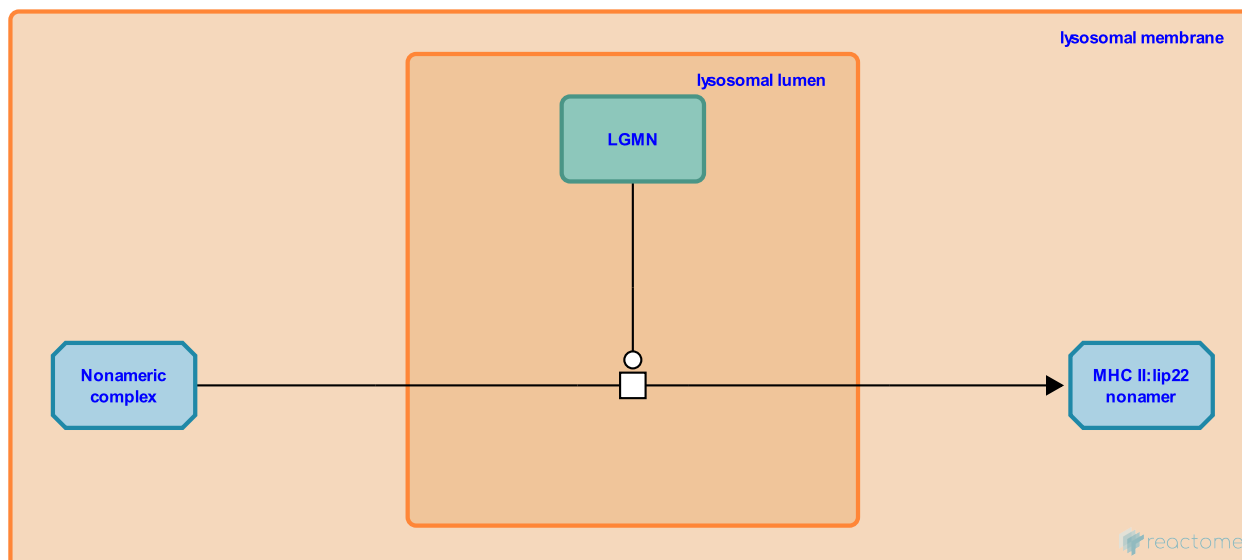
Initial proteolysis of Ii by aspartic proteases to lip22 ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130336

Type: transition

Compartments: lysosomal lumen, lysosomal membrane



Within acidic endocytic compartments Ii is proteolytically cleaved, ultimately freeing the class II peptide-binding groove for loading of antigenic peptides. Ii is degraded in a stepwise manner by a combination of aspartyl and cysteine proteases, following a well defined path with intermediates lip22, lip10 and finally CLIP. The initial Ii cleavage has been ascribed to leupeptin-insensitive cysteine or aspartic proteases, which include aspartyl protease and asparagine endopeptidase (AEP) (Maric et al. 1994, Manoury et al. 2003, Costantino et al. 2008). These proteases generate 22 kDa fragments of Ii (lip22). The trimerization domain of human Ii (residues 134-208) has three possible AEP cleavage sites, Asn148, 165 and 171. Asn171, located at the C-terminal end of helix B, is the demonstrated cleavage site for AEP (Manoury et al. 2003, Jasanoff et al. 1998). This cleavage eliminates the C-terminal trimerization domain of Ii, which causes disassociation of the (MHC II:Ii)₃ nonamer and exposes new cleavage sites in the MHC II:lip22 trimers (Villadangos et al. 1999, Guillaume et al. 2008). The residue numbering of Ii given above is based on Uniprot isoform 1.

Preceded by: [TGN-lysosome vesicle uncoating and release of nonameric complex to lysosome](#), [Trafficking of nonameric complex in the endocytic pathway](#)

Followed by: [Cleavage of lip22 to lip10](#)

Literature references

Costantino, CM., Ploegh, HL., Hafler, DA., Kent, SC., Hang, HC. (2008). Lysosomal cysteine and aspartic proteases are heterogeneously expressed and act redundantly to initiate human invariant chain degradation. *J Immunol*, 180, 2876-85. ↗

Taylor, MD., Blum, JS., Mari?, MA. (1994). Endosomal aspartic proteinases are required for invariant-chain processing. *Proc Natl Acad Sci U S A*, 91, 2171-5. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

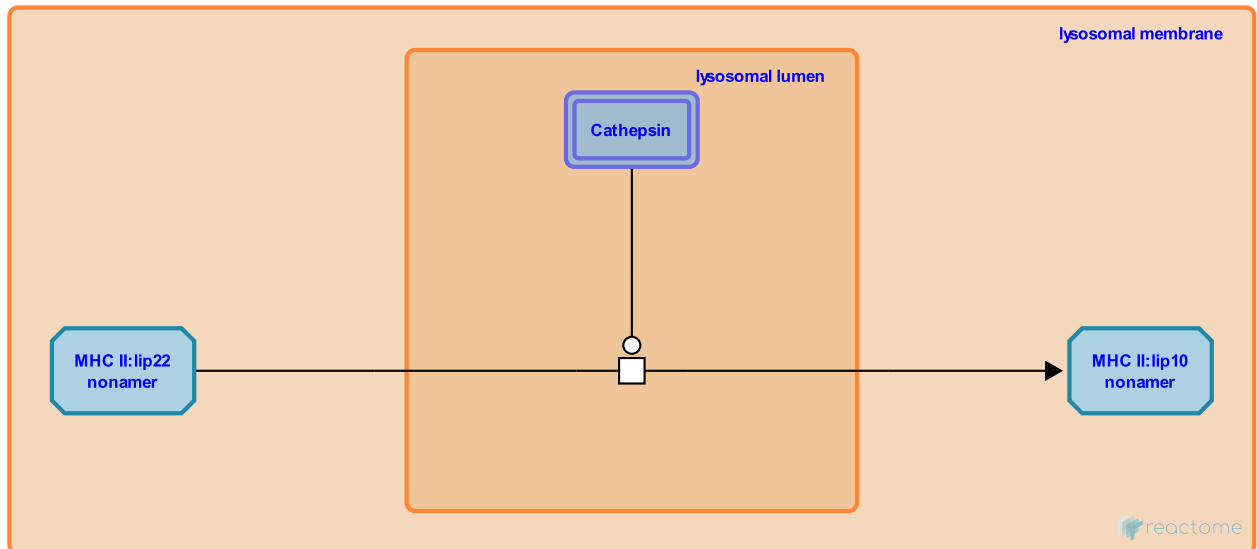
Cleavage of lip22 to lip10 ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130504

Type: transition

Compartments: lysosomal lumen, lysosomal membrane



The cleavage of lip22 occurs in residues 115-125, closer to the C-terminus than CLIP (residues 81-105). The resulting lip10 fragment is approximately 100 residues long and extends just through the C-terminus of the Ii CLIP. The proteases responsible for generating lip10 *in vivo* are not determined. Cysteine proteases like cathepsin S (CatS) are capable of degrading lip22 to lip10 (Bania et al. 2003) but in the presence of LHVS, an inhibitor of CatS, lip22 degradation is still observed, suggesting that other proteases are involved (Villadangos et al. 1997), possibly aspartic proteinases such as cathepsins D and E (Kageyama et al. 1996). The degradation of lip22 may depend on cell type (Bania et al. 2003). The lip22 and lip10 intermediate forms are still maintained as a nonameric complex due to the existence of the last trimerisation domain in the transmembrane region.

Preceded by: [Initial proteolysis of Ii by aspartic proteases to lip22](#)

Followed by: [Generation of CLIP from lip10](#)

Literature references

- Ploegh, HL., Lagaudrière-Gesbert, C., Fiebiger, E., Bryant, PW., Lennon-Duménil, AM. (2002). Proteolysis and antigen presentation by MHC class II molecules. *Adv Immunol*, 80, 71-114. ↗
- Kageyama, T., Yonezawa, S., Ichinose, M., Moriyama, A., Miki, K. (1996). Potential sites for processing of the human invariant chain by cathepsins D and E. *Biochem Biophys Res Commun*, 223, 549-53. ↗
- Villadangos, JA. (2001). Presentation of antigens by MHC class II molecules: getting the most out of them. *Mol Immunol*, 38, 329-46. ↗
- Camosseto, V., Lelouard, H., Pierre, P., Cappello, F., Gatti, E., David, A. et al. (2003). Human cathepsin S, but not cathepsin L, degrades efficiently MHC class II-associated invariant chain in nonprofessional APCs. *Proc Natl Acad Sci U S A*, 100, 6664-9. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neeffes, J.

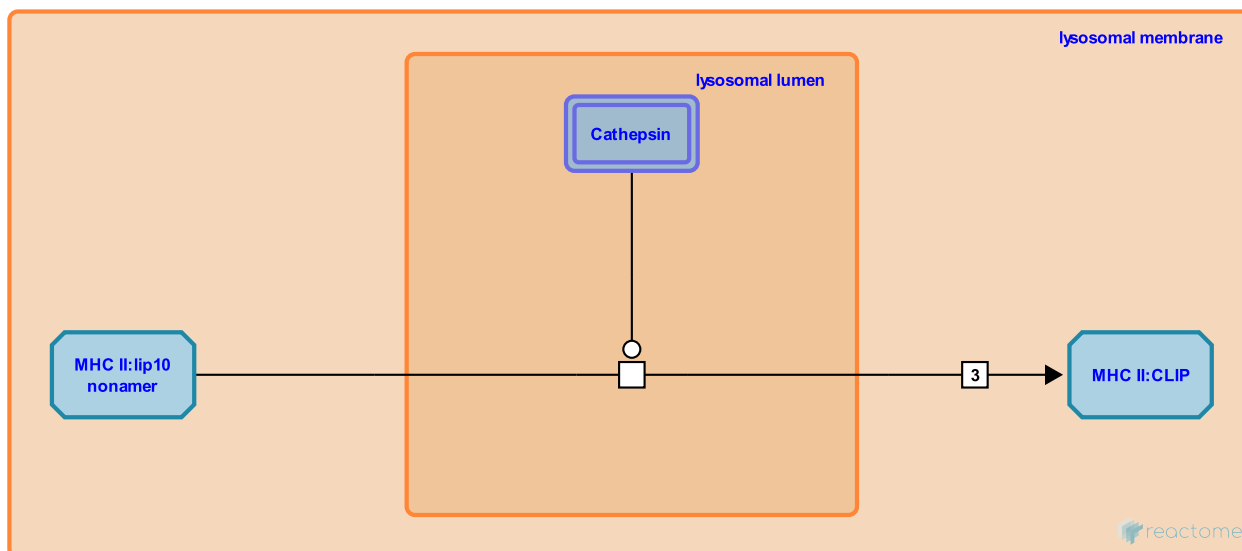
Generation of CLIP from lip10 ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130349

Type: transition

Compartments: lysosomal lumen, lysosomal membrane



The lip10 fragments bound in the nonameric complex are processed leaving only the CLIP fragment (81-105) bound to the MHC II peptide binding groove. Three cysteine proteases have been shown to be capable of digesting lip10, each with a different expression pattern among different APC. Cathepsin (Cat) S digests Ii in B cells and dendritic cells, thymic epithelial cells use Cat L and Cat L, while Cat S and F are active in macrophages (Villadangos, 2001; Bryant et al, 2002). Cat S appears to be the major enzyme involved as demonstrated by the use of specific inhibitors and of knockout experiments (Stumptner-Cuvelette et al. 2002). Following lip10 digestion, the MHC-like molecule HLA-DM induces the exchange of CLIP fragment for a highly diverse array of antigens (Denzin & Cresswell. 1995).

Preceded by: [Cleavage of lip22 to lip10](#)

Followed by: [Disassociation of CLIP from MHC II](#)

Literature references

- Ploegh, HL., Lagaudrière-Gesbert, C., Fiebiger, E., Bryant, PW., Lennon-Duménil, AM. (2002). Proteolysis and antigen presentation by MHC class II molecules. *Adv Immunol*, 80, 71-114. ↗
- Chapman, HA., Ploegh, HL., Bromme, D., Driessen, C., Riese, R., Verhelst, S. et al. (2000). Role for cathepsin F in invariant chain processing and major histocompatibility complex class II peptide loading by macrophages. *J Exp Med*, 191, 1177-86. ↗
- Camosseto, V., Lelouard, H., Pierre, P., Cappello, F., Gatti, E., David, A. et al. (2003). Human cathepsin S, but not cathepsin L, degrades efficiently MHC class II-associated invariant chain in nonprofessional APCs. *Proc Natl Acad Sci U S A*, 100, 6664-9. ↗
- Stumptner-Cuvelette, P., Benaroch, P. (2002). Multiple roles of the invariant chain in MHC class II function. *Biochim Biophys Acta*, 1542, 1-13. ↗
- Villadangos, JA., Farr, A., Peters, C., Wong, P., Ploegh, H., Deussing, J. et al. (1998). Cathepsin L: critical role in Ii degradation and CD4 T cell selection in the thymus. *Science*, 280, 450-3. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

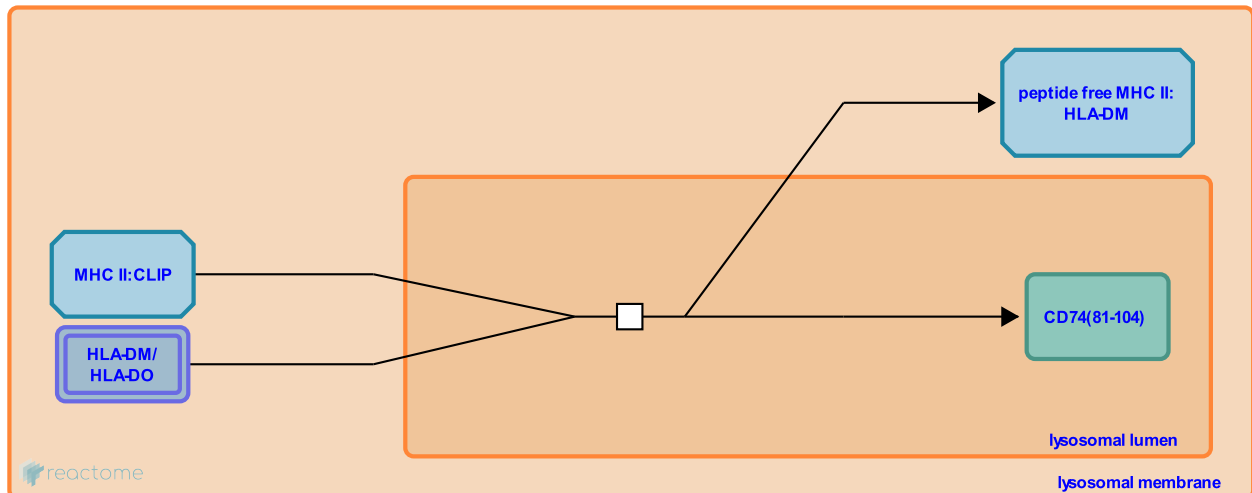
Disassociation of CLIP from MHC II ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213246

Type: transition

Compartments: lysosomal lumen, lysosomal membrane



To gain the capacity to activate antigen-specific T cells, MHC class II-associated CLIP must be exchanged for an antigenic peptide (Kropshofer et al. 1999). There are two CLIP variants in humans: CLIP(long) with 21-26 residues, and CLIP(short) with 14-19 residues. CLIP(long) disassociates rapidly from HLA-DR molecules at endosomal/lysosomal pH, whereas CLIP(short) displays a lower off-rate. The N-terminal 9 residues of CLIP (81-89) facilitate its rapid release (Urban et al. 1994, Kropshofer et al. 1995a, Kropshofer et al. 1995b). The non-classical MHC class II molecule HLA-DM (DM) functions as a mediator of peptide exchange by accelerating the removal of CLIP. DM mediated peptide release involves a direct interaction between DM and the class II molecule. In addition to peptide release, DM also acts as a chaperone for MHC class II molecules in endosomal/lysosomal compartments. It stabilizes the peptide-receptive empty MHC II molecules and prevents them from unfolding and also favors the generation of high-stability peptide-MHC class II complexes by promoting release of low-stability peptide ligands (Kropshofer et al. 1999, Kropshofer et al. 1997). Another non-classical MHC II molecule HLA-DO (DO), only expressed in B-cells and thymic epithelial cells, binds tightly to DM modulating DM activity both negatively and positively, depending on the amount of DO present in an APC. Heterotypic DR-DM-DO complexes are receptive for peptide loading, in these complexes DO does not appear to be inhibitory (Denzin et al. 1997, Kropshofer et al. 1998, Kropshofer et al. 1999).

Preceded by: [Generation of CLIP from lip10](#)

Followed by: [Loading of antigenic peptides](#)

Literature references

- Hammond, C., Sant'Angelo, DB., Surman, MJ., Cresswell, P., Denzin, LK. (1997). Negative regulation by HLA-DO of MHC class II-restricted antigen processing. *Science*, 278, 106-9. ↗
- Chicz, RM., Urban, RG., Strominger, JL. (1994). Selective release of some invariant chain-derived peptides from HLA-DR1 molecules at endosomal pH. *J Exp Med*, 180, 751-5. ↗
- Moldenhauer, G., Armandola, EA., Thery, C., Kropshofer, H., Li, BC., Vogt, AB. et al. (1998). A role for HLA-DO as a co-chaperone of HLA-DM in peptide loading of MHC class II molecules. *EMBO J*, 17, 2971-81. ↗
- Kropshofer, H., Vogt, AB., Hämmerling, GJ. (1995). Structural features of the invariant chain fragment CLIP controlling rapid release from HLA-DR molecules and inhibition of peptide binding. *Proc Natl Acad Sci U S A*, 92, 8313-7. ↗
- Kropshofer, H., Vogt, AB., Stern, LJ., Hämmerling, GJ. (1995). Self-release of CLIP in peptide loading of HLA-DR molecules. *Science*, 270, 1357-9. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

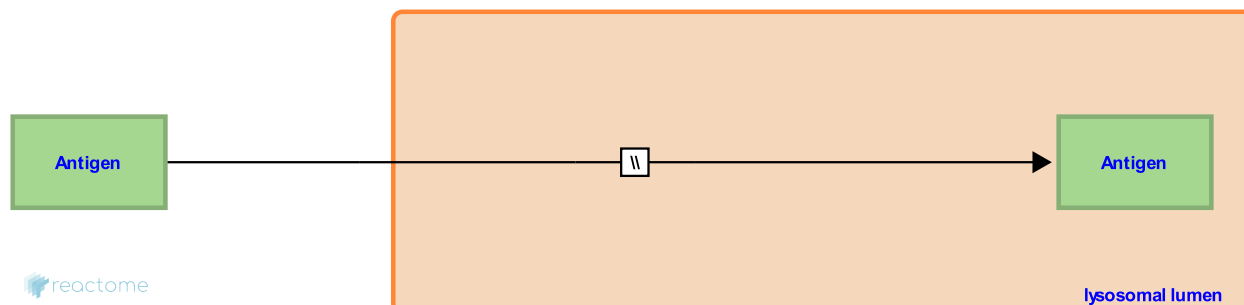
MHC class II antigen internalization ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130627

Type: omitted

Compartments: lysosomal lumen, extracellular region



MHC II typically presents antigens derived from exogenous proteins internalized by APCs such as macrophages, B cells or dendritic cells. Different types of antigen use different routes of internalization. Endocytosis may be specific, mediated by a range of receptors expressed on APC, or may occur by nonspecific mechanisms such as phagocytosis, macropinocytosis or autophagy. Antigens are first loaded into endocytic vesicles and progress along the early endosomes (EE)-late endosomes (LE) lysosomal axis. Antigens are exposed to increasingly acidic, more denaturing and proteolytic conditions (Doherty & McMahon 2009, Underhill & Ozinsky 2002).

Followed by: [Reduction of disulphide bonds in MHC II antigens](#)

Literature references

Mellman, I. (1996). Endocytosis and molecular sorting. *Annu Rev Cell Dev Biol*, 12, 575-625. ↗

Harding, CV., Noss, E., Ramachandra, L., Boom, WH. (2001). Processing of Mycobacterium tuberculosis antigen 85B involves intraphagosomal formation of peptide-major histocompatibility complex II complexes and is inhibited by live bacilli that decrease phagosome maturation. *J Exp Med*, 194, 1421-32. ↗

Harding, CV., Ramachandra, L., Song, R. (1999). Phagosomes are fully competent antigen-processing organelles that mediate the formation of peptide:class II MHC complexes. *J Immunol*, 162, 3263-72. ↗

McMahon, HT., Doherty, GJ. (2009). Mechanisms of endocytosis. *Annu Rev Biochem*, 78, 857-902. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

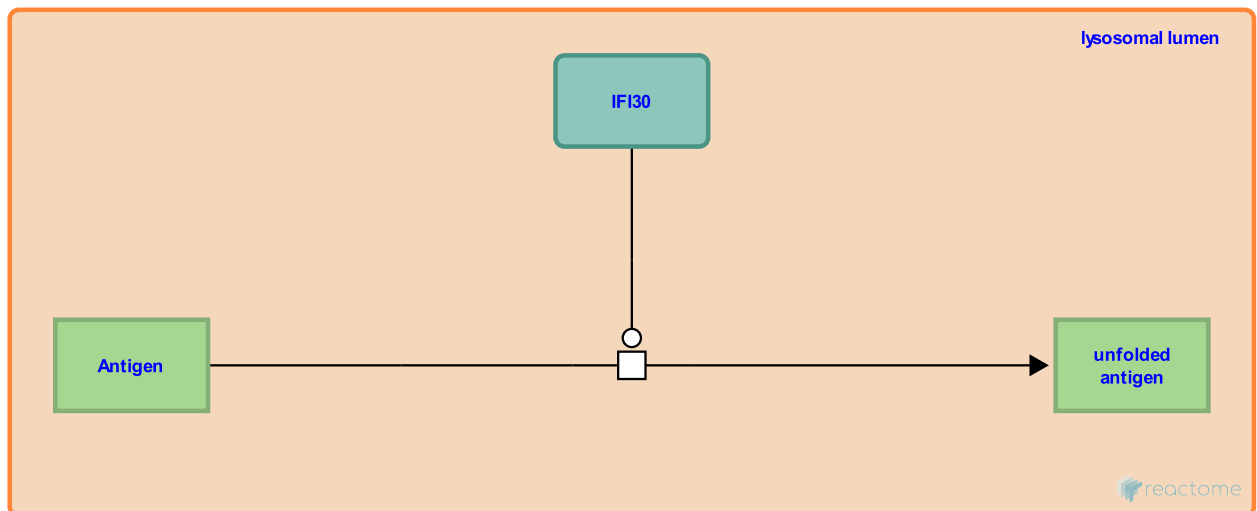
Reduction of disulphide bonds in MHC II antigens ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213240

Type: transition

Compartments: lysosomal lumen



MHC class II epitopes require protein denaturation and removal of intra- and inter-chain disulphide bonds prior to proteolysis. The lysosomal thiol reductase gamma-IFN-inducible lysosomal thiol reductase (GILT) has been shown to facilitate MHC class II-restricted antigen (Ag) processing by breaking disulphide bonds. GILT is constitutively expressed in APCs. The reduction of disulphide bonds by mature GILT is optimal at acidic pH (Hastings et al. 2006, Arunachalam et al. 2000).

Preceded by: [MHC class II antigen internalization](#)

Followed by: [MHC class II antigen processing](#)

Literature references

Arunachalam, B., Phan, UT., Cresswell, P., Geuze, HJ. (2000). Enzymatic reduction of disulfide bonds in lysosomes: characterization of a gamma-interferon-inducible lysosomal thiol reductase (GILT). *Proc Natl Acad Sci U S A*, 97, 745-50. ↗

Lackman, RL., Cresswell, P., Hastings, KT. (2006). Functional requirements for the lysosomal thiol reductase GILT in MHC class II-restricted antigen processing. *J Immunol*, 177, 8569-77. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

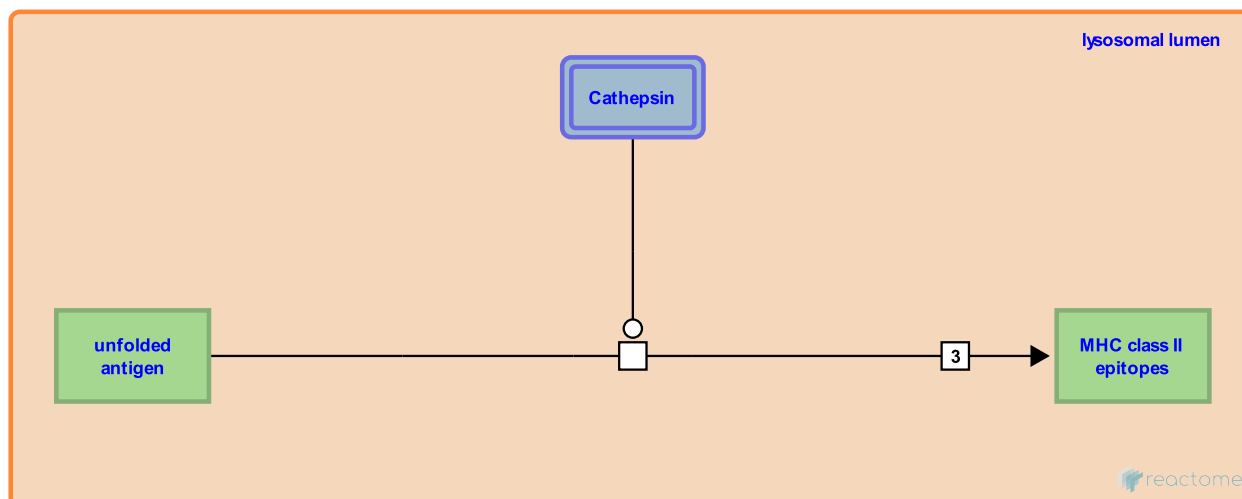
MHC class II antigen processing ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2130706

Type: transition

Compartments: lysosomal lumen



Antigen processing and loading on to MHC class II molecules occurs in late endocytic/lysosomal vesicles, where epitopes which require extensive proteolytic processing are generated (Bryant & Ploegh 2003). These late endosome/lysosomal-like compartments are enriched in MHC II and are referred to as MIICs (MHC class II compartments) (Peters et al. 1991). A variety of lysosomal proteases like cathepsins S, D, B etc. and Asparaginyl endopeptidase (AEP) are suggested to be involved in the processing of antigens to generate CD4⁺ T cell epitopes (Deusing et al. 1998, Shi et al. 1999, Pluger et al. 2002, Watts et al. 2005). An initial cleavage by endopeptidases (AEP) would be necessary to unlock the antigen and allow further trimming of the ends by exopeptidases (Cathepsins). In the acidic environment of the lysosome, cathepsins are generally activated by autocatalytic cleavage of a propeptide which otherwise blocks the active site.

Preceded by: [Reduction of disulphide bonds in MHC II antigens](#)

Followed by: [Loading of antigenic peptides](#)

Literature references

- Ploegh, HL., Villadangos, JA., Peters, C., Deussing, J., Saftig, P., Roth, W. (1998). Cathepsins B and D are dispensable for major histocompatibility complex class II-mediated antigen presentation. *Proc Natl Acad Sci U S A*, 95, 4516-21. ↗
- Himeno, K., Katunuma, N., Maekawa, Y., Sakai, T., Dainichi, T., Asao, T. et al. (2000). Lysosomal cathepsin B plays an important role in antigen processing, while cathepsin D is involved in degradation of the invariant chain in ovalbumin-immunized mice. *Immunology*, 100, 13-20. ↗
- Watts, C., Mazzeo, D., Matthews, SP., Manoury, B., Moss, CX. (2005). Asparaginyl endopeptidase: case history of a class II MHC compartment protease. *Immunol Rev*, 207, 218-28. ↗
- Lautwein, A., Tolosa, E., Krause, S., Driessen, C., Morgalla, M., Mitsdörffer, M. et al. (2003). Antigen processing and presentation in human muscle: cathepsin S is critical for MHC class II expression and upregulated in inflammatory myopathies. *J Neuroimmunol*, 138, 132-43. ↗
- Ploegh, HL., Driessen, C., Plüger, EB., Alfonso, C., Boes, M., Kalbacher, H. et al. (2002). Specific role for cathepsin S in the generation of antigenic peptides in vivo. *Eur J Immunol*, 32, 467-76. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

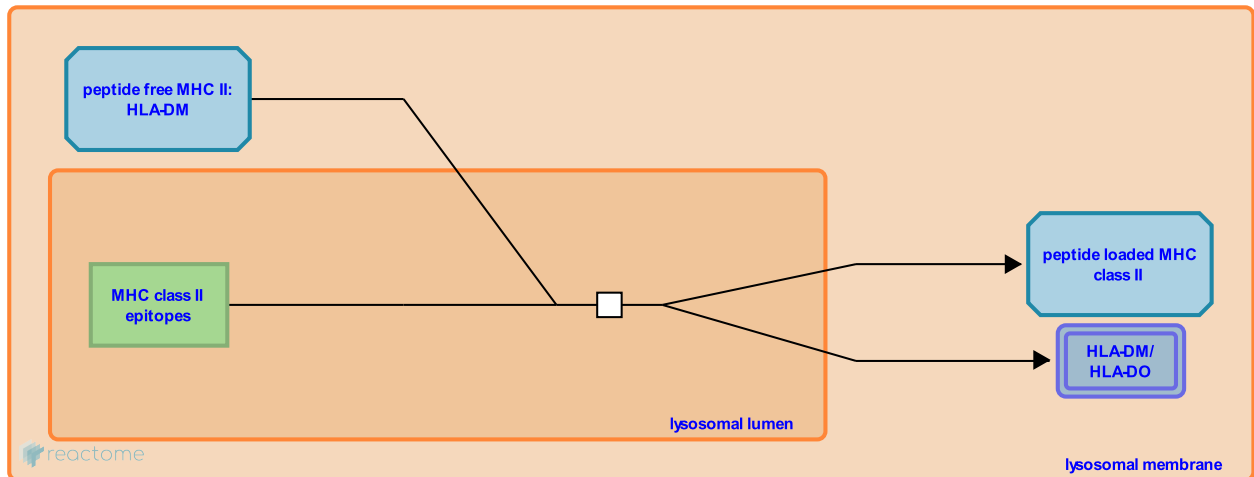
Loading of antigenic peptides ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-2213244

Type: transition

Compartments: lysosomal lumen, lysosomal membrane



In the acidic compartments of MHCs the empty MHC II molecules are protected from unfolding and degradation by HLA-DM (DM). DM acts as a peptide editor, favouring the formation and presentation of long-lived MHC II peptide complexes on the surface of APCs. The intrinsic stability of a ligand determines whether a peptide is resistant or sensitive to DM-mediated release (Kropshofer et al. 1996, Weber et al. 1996). From X-ray structure analysis it is known that two types of forces contribute to the intrinsic stability of class II-peptide complexes: i) interactions of the anchor side chains of the peptides with specificity pockets of polymorphic residues of the peptide binding groove of MHC II and ii) hydrogen bonds between the peptide backbone and conserved residues of the peptide binding grooves (Stern et al. 1994, Kropshofer et al. 1999). Naturally-processed antigenic peptides 14-16 residues in length with many anchor residues and few destabilizing residues (glycine and proline) at non-anchor positions are the most resistant to DM-mediated release (Radrizzani et al. 1999, Kropshofer et al. 1999).

Preceded by: [Disassociation of CLIP from MHC II](#), [MHC class II antigen processing](#)

Followed by: [Transport of antigen loaded MHC II molecules to surface](#)

Literature references

- Sinigaglia, F., Kropshofer, H., Gallazzi, F., Sturniolo, T., Radrizzani, L., Vogt, AB. et al. (1999). Identification of destabilizing residues in HLA class II-selected bacteriophage display libraries edited by HLA-DM. *Eur J Immunol*, 29, 660-8. ↗
- Jensen, PE., Weber, DA., Evavold, BD. (1996). Enhanced dissociation of HLA-DR-bound peptides in the presence of HLA-DM. *Science*, 274, 618-20. ↗
- Kropshofer, H., Vogt, AB., Hämmerling, GJ. (1999). The impact of the non-classical MHC proteins HLA-DM and HLA-DO on loading of MHC class II molecules. *Immunol Rev*, 172, 267-78. ↗
- Gorga, JC., Jardetzky, TS., Urban, RG., Strominger, JL., Brown, JH., Stern, LJ. et al. (1994). Crystal structure of the human class II MHC protein HLA-DR1 complexed with an influenza virus peptide. *Nature*, 368, 215-21. ↗
- Moldenhauer, G., Kropshofer, H., Blum, JS., Vogt, AB., Hammer, J., Hämmerling, GJ. (1996). Editing of the HLA-DR-peptide repertoire by HLA-DM. *EMBO J*, 15, 6144-54. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

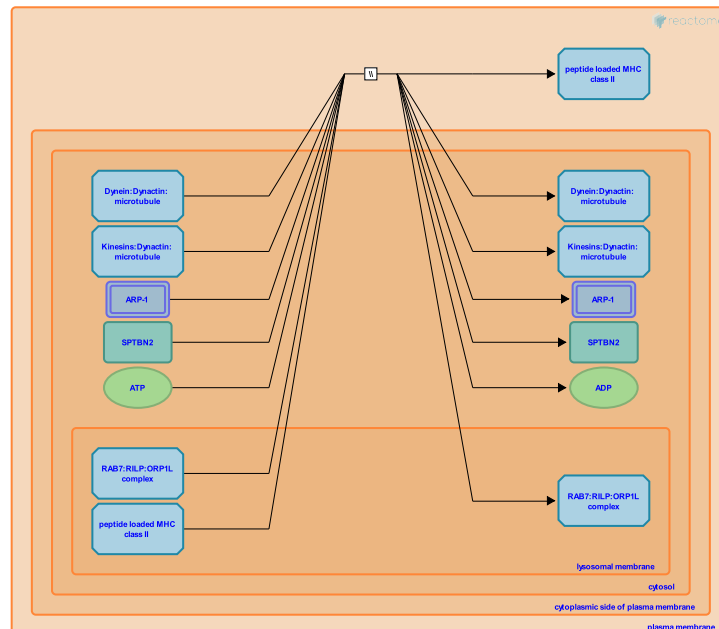
Transport of antigen loaded MHC II molecules to surface ↗

Location: MHC class II antigen presentation

Stable identifier: R-HSA-2213248

Type: omitted

Compartments: plasma membrane, cytosol, lysosomal membrane



Once MHC class II-peptide complexes are formed, they must be transported back to the cell surface. It is unclear how this occurs. LEs/lysosomes with peptide loaded MHC II molecules may move in a bidirectional manner in a stop-and-go fashion along microtubules to the plasma membrane, driven by the activities of the oppositely-directed motor proteins dynein and kinesin (Wubbolts et al. 1996, 1999, Chow et al. 2002, Rocha & Neefjes 2007). Ultimately, LEs/lysosomes fuse to the plasma membrane delivering the MHC II-peptide complexes to the surface (Raposo et al. 1996, Rocha & Neefjes 2007). RAB7-GTP present on LEs/lysosome membrane interacts with Rab7-interacting lysosomal protein (RILP) and oxysterol-binding protein-related protein 1L (ORP1L) to form a tripartite RILP-Rab7-ORP1L complex. RILP binds to the p150 dynactin subunit to recruit the dynein or kinesin motor proteins. ORP1L recruits this complex to betaIII spectrin domains, which appears to be critical for dynein motor activation and transport of LEs/lysosome vesicles to the cell periphery (Johansson et al. 2007, Rocha & Neefjes 2008).

Preceded by: Loading of antigenic peptides

Literature references

- Neefjes, J., Rocha, N. (2008). MHC class II molecules on the move for successful antigen presentation. *EMBO J*, 27, 1-5. ↗
- Neefjes, J., Reits, E., Vallee, RB., Fernandez-Borja, M., Dusseljee, S., Jordens, I. et al. (1999). Opposing motor activities of dynein and kinesin determine retention and transport of MHC class II-containing compartments. *J Cell Sci*, 112, 785-95. ↗
- Harding, CV., Liejendekker, R., Stoorvogel, W., Nijman, HW., Geuze, HJ., Melief, CJ. et al. (1996). B lymphocytes secrete antigen-presenting vesicles. *J Exp Med*, 183, 1161-72. ↗
- Janssen, H., Janssen, L., Rocha, N., Zwart, W., Neefjes, J., Kuijl, C. et al. (2009). Cholesterol sensor ORP1L contacts the ER protein VAP to control Rab7-RILP-p150 Glued and late endosome positioning. *J. Cell Biol.*, 185, 1209-25. ↗
- Neefjes, J., Tulp, A., Calafat, J., Fernandez-Borja, M., Janssen, H., Verwoerd, D. et al. (1996). Direct vesicular transport of MHC class II molecules from lysosomal structures to the cell surface. *J Cell Biol*, 135, 611-22. ↗

Editions

2012-02-21	Authored, Edited	Garapati, P V.
2012-05-14	Reviewed	Neefjes, J.

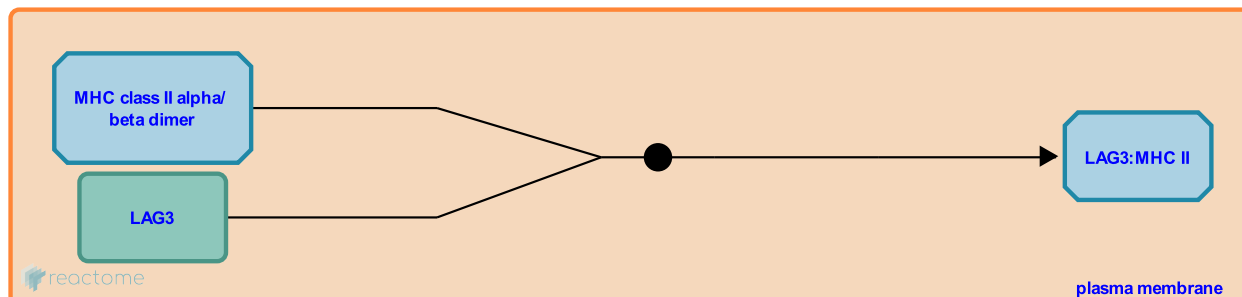
LAG3 (CD233) binds MHC II ↗

Location: [MHC class II antigen presentation](#)

Stable identifier: R-HSA-8856157

Type: binding

Compartments: plasma membrane



Melanomas often express MHC II molecules along with tumor-associated and tumor-specific Ags, which could make these tumors detectable and eliminated by the immune system. However the expression of MHC II molecules by melanoma cells has been instead associated with poor prognosis (Ruiter et al. 1991, Deffrennes et al. 2001, Ostmeier et al. 2001, Martins et al. 2009). The exact role that MHC II might have in melanoma progression is unclear; it was suggested that MHC II can be involved in the escape of melanoma cells from immune surveillance. Lymphocyte-activation gene 3 (LAG3) belongs to Ig superfamily and is expressed by various subsets of tumor-infiltrating leukocytes. LAG3 is a natural ligand for MHC II and binds MHC II with a much higher avidity than CD4. LAG3 protects MHC II positive melanoma cells from apoptosis. Hemon et al proposes that LAG3-MHC II molecular interaction as a novel pathway enabling melanoma cells not only to escape immune attack but also to counter drug effects and to survive (Hemon et al. 2011).

Literature references

Charron, D., Brignone, C., Ramgolam, K., Triebel, F., Michel, L., Aoudjit, F. et al. (2011). MHC class II engagement by its ligand LAG-3 (CD223) contributes to melanoma resistance to apoptosis. *J. Immunol.*, 186, 5173-83. ↗

Editions

2016-02-09	Authored, Edited	Garapati, P V.
2016-09-14	Reviewed	Meldal, BH.

Table of Contents

Introduction	1
❏ MHC class II antigen presentation	2
➤ Formation of MHC II alpha beta heterodimer	3
➤ Interaction of invariant chain trimer and MHC II alpha beta dimer	4
➤ Formation of nonameric complex	6
➤ Dissociation of CANX from nonameric complex	7
➤ Formation of COPII vesicle	8
➤ Fusion of COPII vesicle with Golgi complex	9
➤➤ Transport of MHC II:Ii complex along Golgi to TGN	10
➤➤ TGN-lysosomal vesicle coat assembly	11
➤ Dissociation of Arf1:GDP, AP-1 Clathrin coated nonameric complex	13
➤ Translocation of TGN-lysosome vesicle to lysosome	15
➤ TGN-lysosome vesicle uncoating and release of nonameric complex to lysosome	16
➤➤ Transport of MHC II:Ii complex to plasma membrane	17
➤➤ Insertion of MHC II:Ii complex in to the plasma membrane	18
➤ Recruitment of clathrin coated vesicle by Ii	19
➤➤ Internalization of MHC II:Ii clathrin coated vesicle	20
➤ Uncoating of clathrin-coated vesicles and fusion with endosomes	21
➤➤ Trafficking of nonameric complex in the endocytic pathway	22
➤ Initial proteolysis of Ii by aspartic proteases to lip22	23
➤ Cleavage of lip22 to lip10	24
➤ Generation of CLIP from lip10	25
➤ Disassociation of CLIP from MHC II	26
➤➤ MHC class II antigen internalization	28
➤ Reduction of disulphide bonds in MHC II antigens	29
➤ MHC class II antigen processing	30
➤ Loading of antigenic peptides	31
➤➤ Transport of antigen loaded MHC II molecules to surface	32
➤ LAG3 (CD233) binds MHC II	34
Table of Contents	35