Initial proteolyis of Ii by aspartic proteases to lip22

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02/05/2024

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. ↗

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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. ↗

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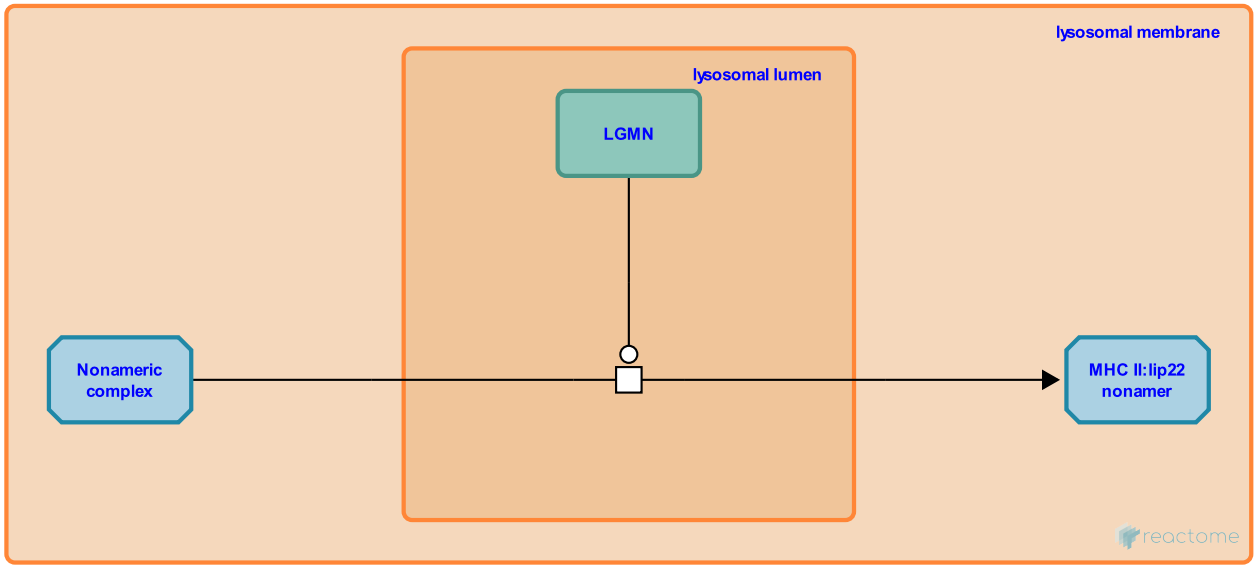
Stable identifier: R-HSA-2130336

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.

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. ↗

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Editions

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