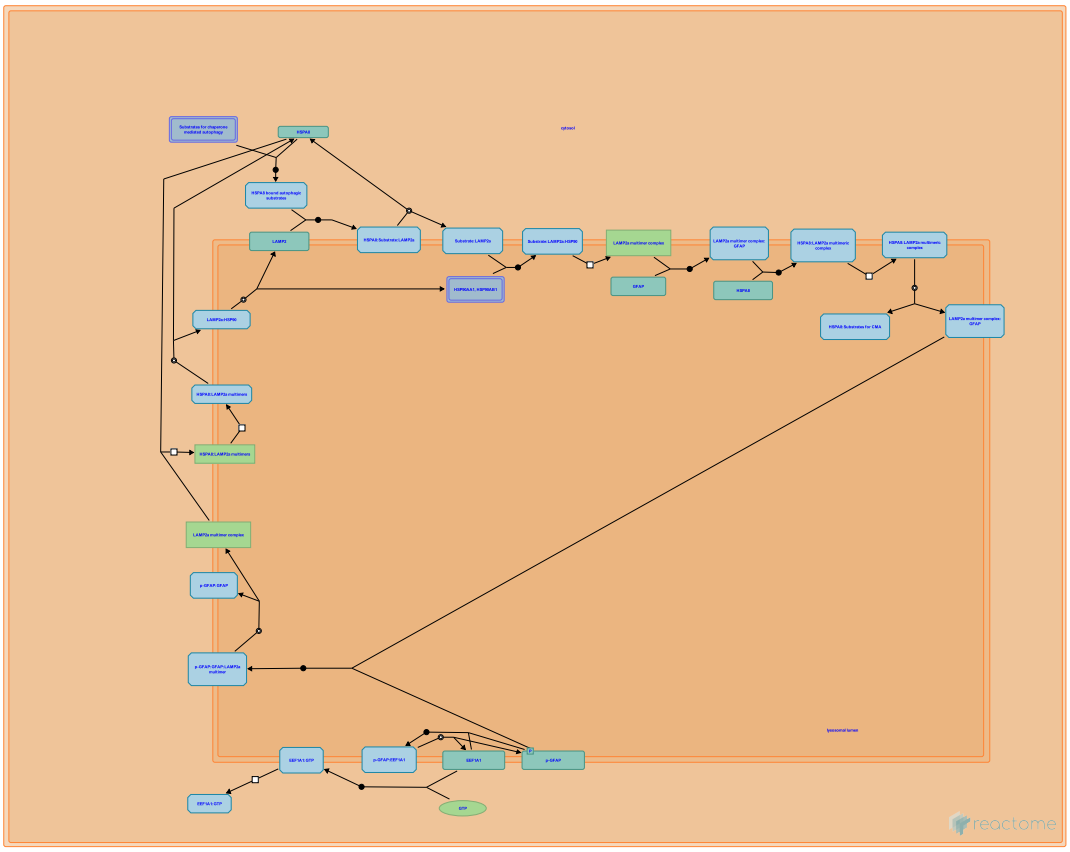
# Chaperone Mediated Autophagy



Metzakopian, E., Varusai, TM.

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



18/08/2021

# 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.

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. ↗

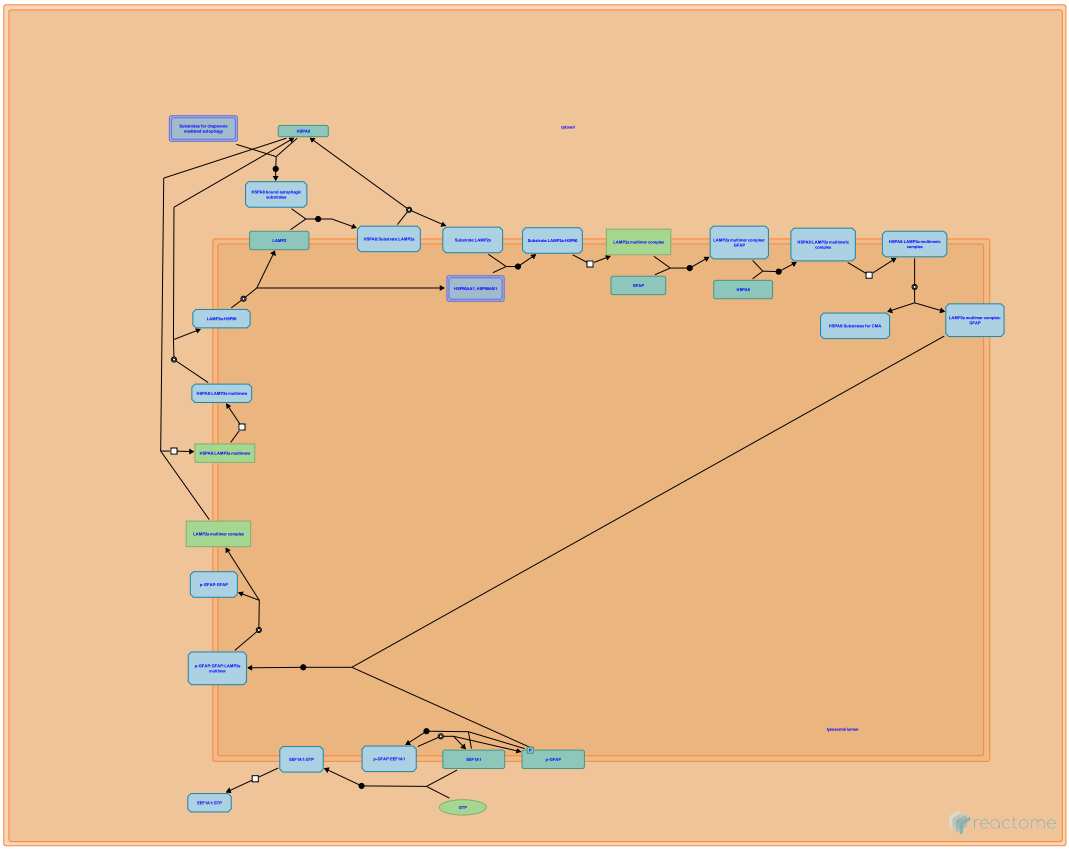
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

## Chaperone Mediated Autophagy ↗

**Stable identifier:** R-HSA-9613829

**Compartments:** cytosol, lysosomal lumen, lysosomal membrane



In contrary to the vesicle-mediated macroautophagy, the chaperone mediated mechanism of autophagy selectively targets individual proteins to the lysosome for degradation. Chaperones bind intracellular proteins based on recognition motifs and transports them from the cytosol to the lysosomal membrane. Subsequently, the protein is translocated into the lumen for digestion (Cuervo A M et al. 2014, Kaushik S et al. 2018).

## Literature references

Cuervo, AM., Wong, E. (2014). Chaperone-mediated autophagy: roles in disease and aging. *Cell Res., 24*, 92-104. ↗

## Editions

| | | |
|---|---|---|
| 2019-02-21 | Authored | Varusai, TM. |
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| 2019-10-31 | Revised | Varusai, TM. |
| 2019-11-08 | Edited | Varusai, TM. |

## HSPA8 binds substrate ↗

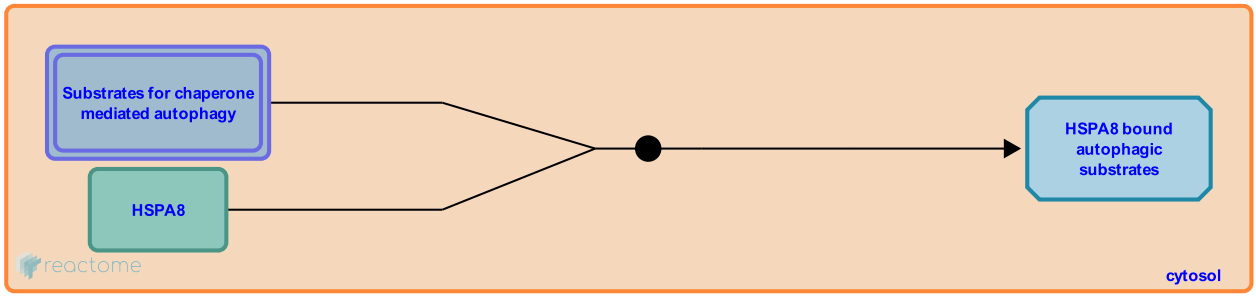
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9615721

**Type:** binding

**Compartments:** cytosol

**Inferred from:** Hspa8 binds Rnase1 (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in the lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) acts as the constitutive chaperone that binds substrate proteins in the cytosol. HSPA8 recognizes a motif based on the charge of the amino acids (Chiang H et al. 1989, Dice JF et al. 1990). This allows the motif to have multiple sequence possibilities and also create a motif through post-translational modifications such as phosphorylation and acetylation. Once bound with HSPA8, the substrates are targeted to the lysosome or endosome.

**Preceded by:** HSPA8 dissociates from LAMP2a, HSPA8 dissociates from LAMP2A-bound substrate

**Followed by:** HSPA8:Substrate binds LAMP2a

## Literature references


Chiang, HL., Terlecky, SR., Plant, CP., Dice, JF. (1989). A role for a 70-kilodalton heat shock protein in lysosomal degradation of intracellular proteins. *Science, 246*, 382-5. ↗

Dice, JF. (1990). Peptide sequences that target cytosolic proteins for lysosomal proteolysis. *Trends Biochem. Sci., 15*, 305-9. ↗

Kaushik, S., Cuervo, AM. (2015). Degradation of lipid droplet-associated proteins by chaperone-mediated autophagy facilitates lipolysis. *Nat. Cell Biol., 17*, 759-70. ↗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| 2019-11-08 | Edited | Varusai, TM. |

## HSPA8:Substrate binds LAMP2a ↗

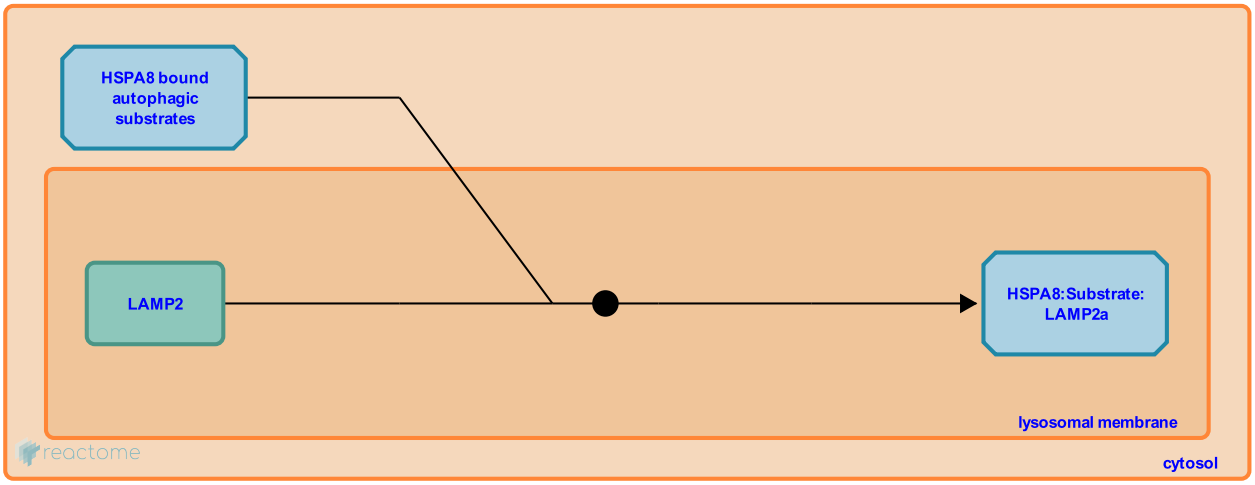
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9620197

**Type:** binding

**Compartments:** lysosomal membrane, cytosol

**Inferred from:** Hspa8:Rnase1 binds Lamp2a (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) acts as the constitutive chaperone that binds substrates in the cytosol. Consequently, the Hspa8:Substrate complex translocates from cytosol to lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a) (Cuervo AM and Dice JF. 1996). Four positively charged amino acids in the cytosolic tail of the LAMP2a isoform is known to regulate the binding mechanism (Cuervo AM and Dice JF. 2000). Experiments confirming this binding were performed on rat models.

**Preceded by:** HSPA8 binds substrate, HSP90 dissociates from LAMP2a

**Followed by:** HSPA8 dissociates from LAMP2A-bound substrate

### Literature references

Cuervo, AM., Dice, JF. (1996). A receptor for the selective uptake and degradation of proteins by lysosomes. *Science, 273*, 501-3. ↗

Cuervo, AM., Dice, JF. (2000). Unique properties of lamp2a compared to other lamp2 isoforms. *J. Cell. Sci., 113*, 4441-50. ↗

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## HSPA8 dissociates from LAMP2A-bound substrate ↗

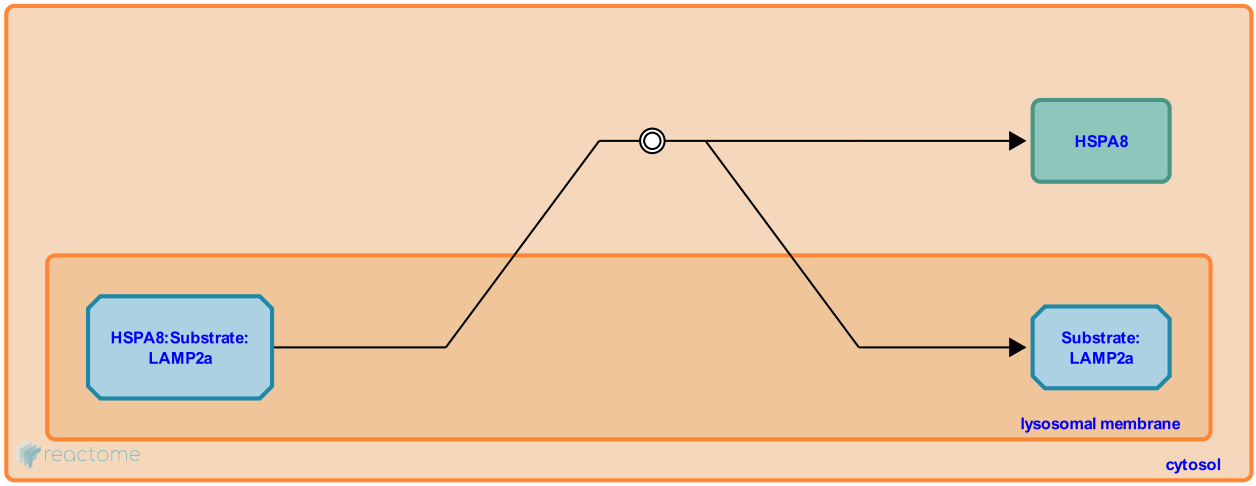
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9622840

**Type:** dissociation

**Compartments:** cytosol, lysosomal membrane

**Inferred from:** Hspa8 dissociates from Lamp2a-bound substrate (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) acts as the constitutive chaperone that binds KFERQ-domain containing substrates in the cytosol. Consequently, the Hspa8:Substrate complex translocates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Post-binding, HSPA8 is released from the complex to allow multimerization of LAMP2a and internalization of the substrate (Bandyopadhyay U et al. 2008). Experiments confirming this binding were performed on rat models.

**Preceded by:** HSPA8:Substrate binds LAMP2a

**Followed by:** Substrate:LAMP2a binds HSP90, HSPA8 binds LAMP2a multimers, HSPA8 binds substrate

## Literature references

Bandyopadhyay, U., Kaushik, S., Varticovski, L., Cuervo, AM. (2008). The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell. Biol., 28*, 5747-63. ↗

Kaushik, S., Cuervo, AM. (2018). The coming of age of chaperone-mediated autophagy. *Nat. Rev. Mol. Cell Biol., 19*, 365-381. ↗

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## Substrate:LAMP2a binds HSP90 ↗

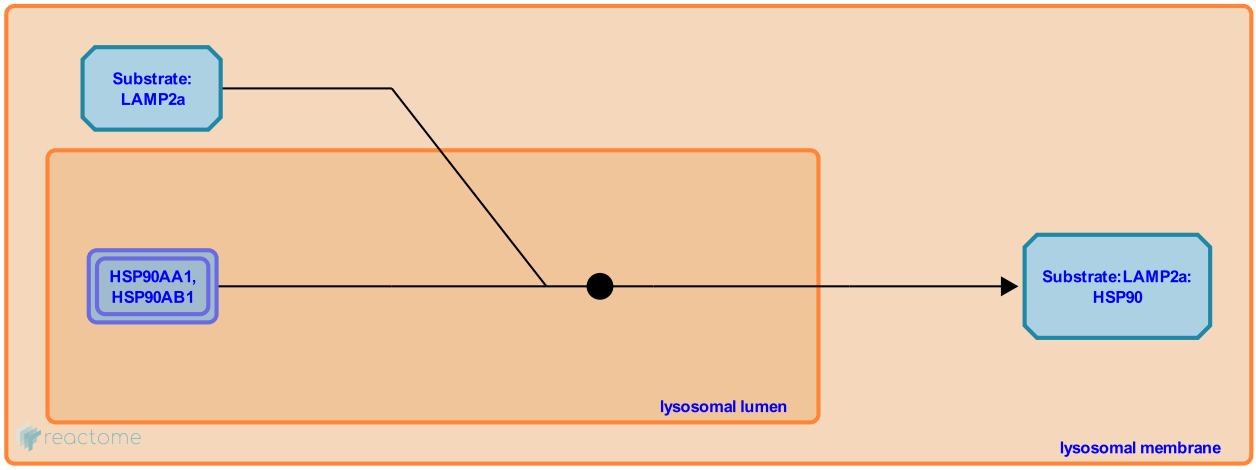
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9622831

**Type:** binding

**Compartments:** lysosomal lumen, lysosomal membrane

**Inferred from:** Substrate:Lamp2a binds Hsp90 (Rattus norvegicus)




Heat shock cognate 71 kDa protein (HSPA8) translocates substrates from cytosol to lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). HSPA8 is then released from this complex. Subsequently, Heat shock protein HSP 90 binds to the lysosomal luminal end of LAMP2a (Bandyopadhyay U et al. 2008). This facilitates the multimerization of LAMP2a and internalization of substrate into the lumen. Experiments confirming this binding were performed on rat models.

**Preceded by:** HSPA8 dissociates from LAMP2A-bound substrate, HSP90 dissociates from LAMP2a

**Followed by:** Substrate:LAMP2a:HSP90 polymerizes

## Literature references


Bandyopadhyay, U., Kaushik, S., Varticovski, L., Cuervo, AM. (2008). The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell. Biol., 28*, 5747-63. ↗

Kaushik, S., Cuervo, AM. (2018). The coming of age of chaperone-mediated autophagy. *Nat. Rev. Mol. Cell Biol., 19*, 365-381. ↗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## Substrate:LAMP2a:HSP90 polymerizes ↗

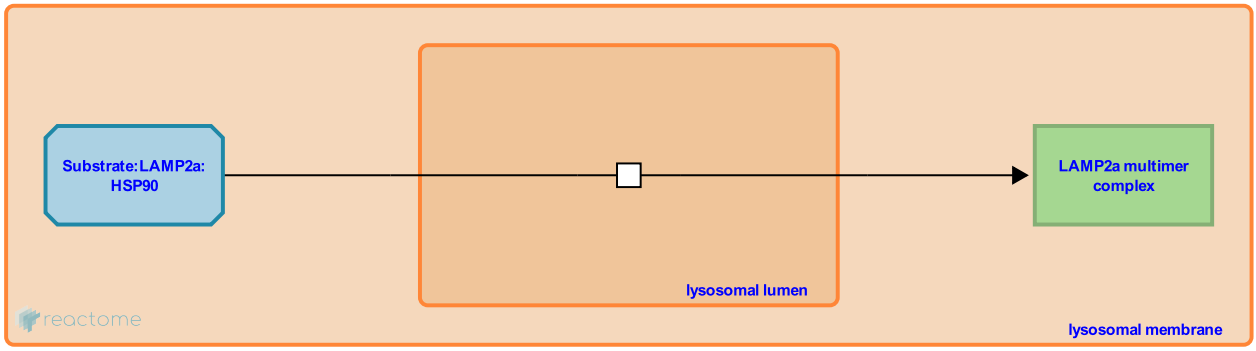
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9624158

**Type:** transition

**Compartments:** lysosomal lumen, lysosomal membrane

**Inferred from:** Substrate:Lamp2a:Hsp90 polymerizes (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in the lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) acts as the constitutive chaperone that binds KFERQ-domain containing substrates in the cytosol. Consequently, the Hspa8:Substrate complex translocates from cytosol to lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, HSPA8 is released and Heat shock protein HSP 90 binds to the lysosomal luminal end of LAMP2a. Binding of HSP90 stabilizes LAMP2 to multimerize into a 700 kDa complex (Bandyopadhyay U et al. 2008). This facilitates the internalization of substrate into the lumen. Experiments confirming this binding were performed on rat models.

**Preceded by:** Substrate:LAMP2a binds HSP90

**Followed by:** GFAP binds LAMP2a multimer

## Literature references

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

Bandyopadhyay, U., Kaushik, S., Varticovski, L., Cuervo, AM. (2008). The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell. Biol., 28*, 5747-63. ↗

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## GFAP binds LAMP2a multimer ↗

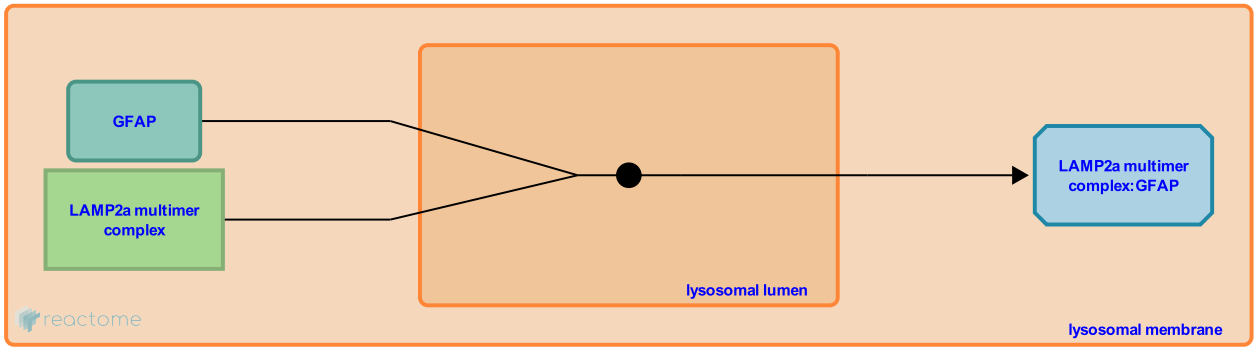
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9625197

**Type:** binding

**Compartments:** lysosomal lumen, lysosomal membrane

**Inferred from:** Gfap binds Lamp2 multimer (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in the lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) acts as the constitutive chaperone that binds KFERQ-domain containing substrates in the cytosol. Consequently, the HSPA8:Substrate complex translocates from cytosol to lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, HSPA8 is released and Heat shock protein HSP 90 binds to the lysosomal luminal end of LAMP2a. This LAMP2a complex then multimerizes into a 700 kDa entity and is stabilized by the binding of Glial fibrillary acidic protein (GFAP) (Bandyopadhyay U et al. 2010). Subsequently, the substrate is unfolded and internalized into the lumen. Experiments confirming this binding were performed on rat models.

**Preceded by:** Substrate:LAMP2a:HSP90 polymerizes

**Followed by:** Unfolded substrate in LAMP2a multimeric complex binds HSPA8

### Literature references

Kaushik, S., Bandyopadhyay, U., Sridhar, S., Kiffin, R., Martinez-Vicente, M., Kon, M. et al. (2011). Chaperone-mediated autophagy at a glance. *J. Cell. Sci., 124*, 495-9. ↗

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

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## Unfolded substrate in LAMP2a multimeric complex binds HSPA8 ↗

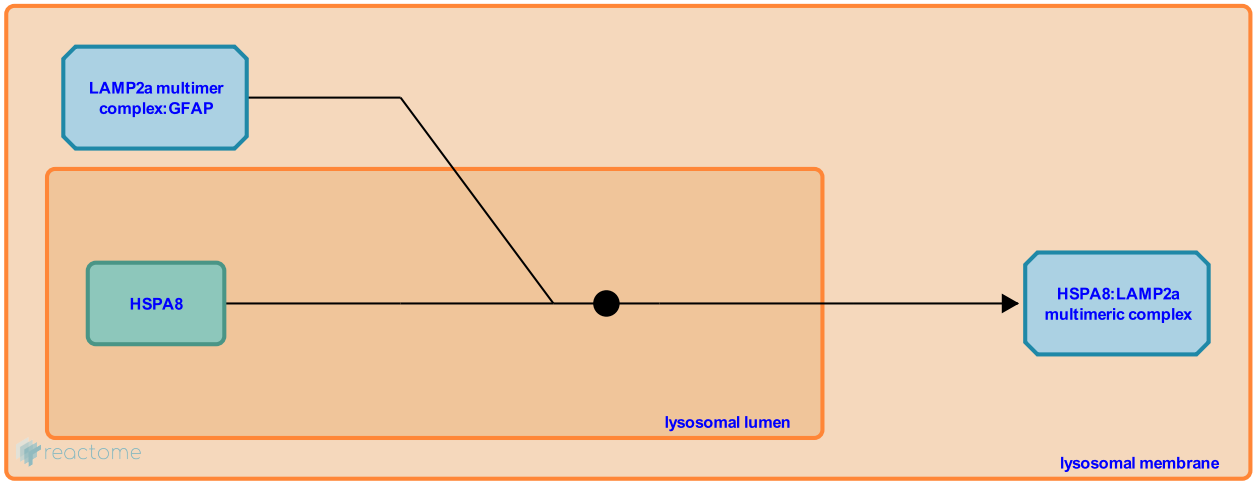
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9625196

**Type:** binding

**Compartments:** lysosomal lumen, lysosomal membrane

**Inferred from:** Unfolded substrate in Lamp2 multimeric complex binds Hspa8 (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in the lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) acts as the constitutive chaperone that binds a KFERQ-domain containing substrate in the cytosol and translocates to lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, Hspa8 is released and Heat shock protein HSP90 binds to the lysosomal luminal end of LAMP2a. The LAMP2a complex then multimerizes and stabilizes. Now, the substrate unfolds and binds to HSPA8 in the lysosomal lumen (Agarraberes FA et al. 1997, Cuervo AM et al. 1997). Subsequently, the substrate is internalized and degraded in the lumen. Experiments confirming this interaction were performed in rats.

**Preceded by:** GFAP binds LAMP2a multimer

**Followed by:** HSPA8 transports unfolded substrate to lysosomal lumen for degradation

### Literature references

Cuervo, AM., Dice, JF., Knecht, E. (1997). A population of rat liver lysosomes responsible for the selective uptake and degradation of cytosolic proteins. *J. Biol. Chem., 272*, 5606-15. ↗

Agarraberes, FA., Terlecky, SR., Dice, JF. (1997). An intralysosomal hsp70 is required for a selective pathway of lysosomal protein degradation. *J. Cell Biol., 137*, 825-34. ↗

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## HSPA8 transports unfolded substrate to lysosomal lumen for degradation ↗

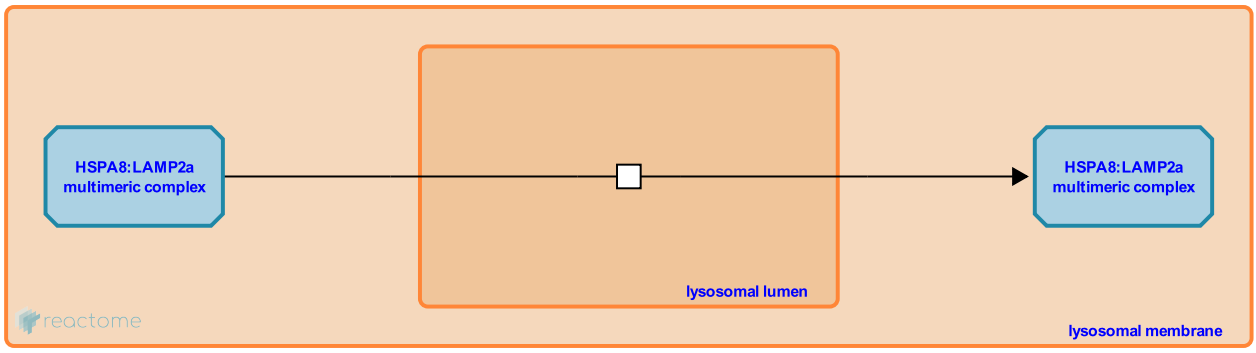
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9625188

**Type:** transition

**Compartments:** lysosomal lumen, lysosomal membrane

**Inferred from:** Hspa8 transports unfolded substrate to lysosomal lumen for degradation (Rattus norvegicus)




Heat shock cognate 71 kDa protein (HSPA8) translocates substrates from the cytosol to the lysosomal membrane. Subsequently, the substrate unfolds and binds to HSPA8 in the lysosomal lumen. HSPA8 facilitates the transport of the unfolded substrate to the lumen where it is then degraded (Agarraberes FA et al. 1997, Cuervo AM et al. 1997).

**Preceded by:** Unfolded substrate in LAMP2a multimeric complex binds HSPA8

**Followed by:** HSPA8:Substrate dissociates from LAMP2a multimer

### Literature references

Cuervo, AM., Dice, JF., Knecht, E. (1997). A population of rat liver lysosomes responsible for the selective uptake and degradation of cytosolic proteins. *J. Biol. Chem., 272*, 5606-15. ↗

Agarraberes, FA., Terlecky, SR., Dice, JF. (1997). An intralysosomal hsp70 is required for a selective pathway of lysosomal protein degradation. *J. Cell Biol., 137*, 825-34. ↗

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## HSPA8:Substrate dissociates from LAMP2a multimer ↗

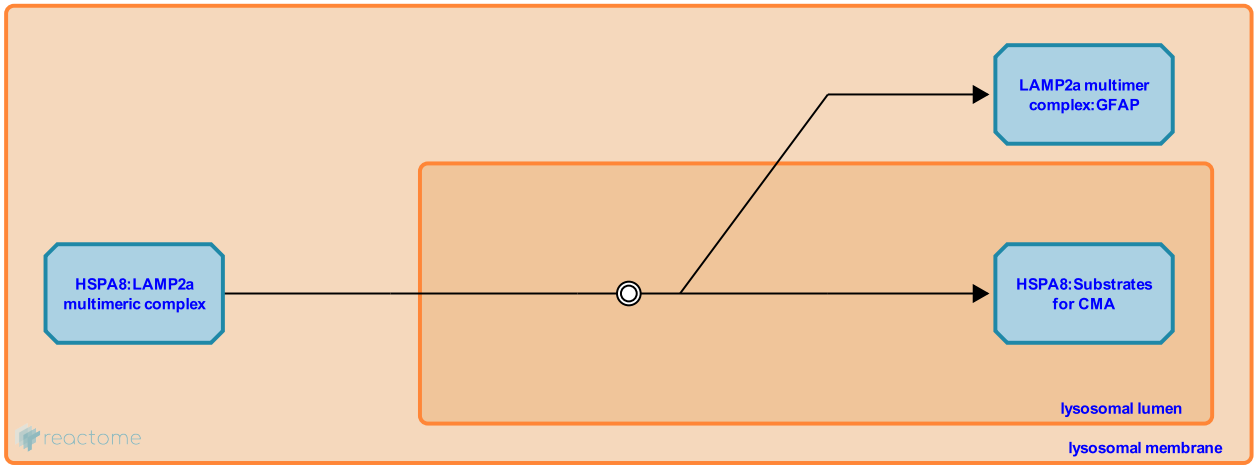
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626060

**Type:** dissociation

**Compartments:** lysosomal lumen, lysosomal membrane

**Inferred from:** Hspa8:Substrate dissociates from Lamp2 multimer (Rattus norvegicus)




Heat shock cognate 71 kDa protein (HSPA8) translocates substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). The LAMP2a complex then multimerizes and stabilizes. Subsequently, the substrate unfolds and translocates to the lumen. The substrate bound HSPA8 then dissociates from LAMP2a multimer (Agarraberes FA et al. 1997, Cuervo AM et al. 1997). The function of LAMP2a multimer is now complete and starts to disassemble.

**Preceded by:** HSPA8 transports unfolded substrate to lysosomal lumen for degradation

**Followed by:** pGFAP binds GFAP in LAMP2a multimer

### Literature references

Cuervo, AM., Dice, JF., Knecht, E. (1997). A population of rat liver lysosomes responsible for the selective uptake and degradation of cytosolic proteins. *J. Biol. Chem., 272*, 5606-15. ↗

Agarraberes, FA., Terlecky, SR., Dice, JF. (1997). An intralysosomal hsp70 is required for a selective pathway of lysosomal protein degradation. *J. Cell Biol., 137*, 825-34. ↗

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## p-GFAP binds EEF1A1 ↗

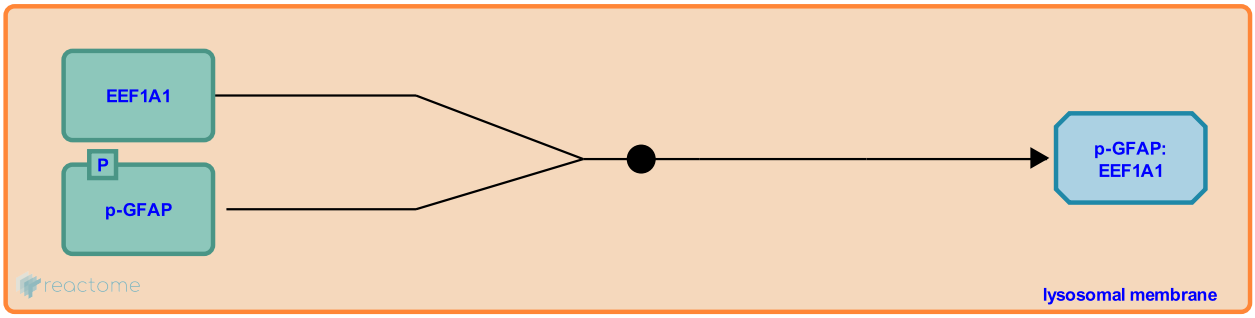
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626046

**Type:** binding

**Compartments:** lysosomal membrane

**Inferred from:** p-Gfap binds Eef1a1 (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex stabilized with the aid of HSP90 and glial fibrillary acidic protein (GFAP). This multimer allows the transfer of substrate into the lumen. The stability of this complex is regulated by the dynamics of GFAP and elongation factor 1α (EEF1A1). During autophagy, a phosphorylated version of GFAP remains bound to EEF1A1 (Bandyopadhyay U et al. 2010, Arias E et al. 2015). Experiments confirming this binding were performed in rats.

**Preceded by:** EEF1A1 dissociates from p-GFAP

**Followed by:** EEF1A1 dissociates from p-GFAP

### Literature references

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

Arias, E., Koga, H., Diaz, A., Mocholi, E., Patel, B., Cuervo, AM. (2015). Lysosomal mTORC2/PHLPP1/Akt Regulate Chaperone-Mediated Autophagy. *Mol. Cell, 59*, 270-84. ↗

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## EEF1A1 dissociates from p-GFAP ↗

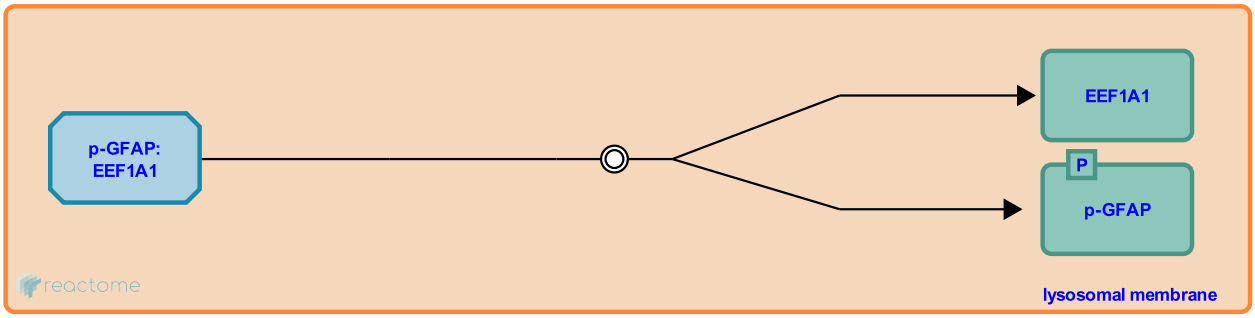
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626034

**Type:** dissociation

**Compartments:** lysosomal membrane

**Inferred from:** Eef1a1 dissociates from p-Gfap (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex stabilized with the aid of HSP90 and glial fibrillary acidic protein (GFAP). This multimer allows the transfer of substrate into the lumen. The stability of this complex is regulated by the dynamics of GFAP and elongation factor 1α (EEF1A1). During autophagy, a phosphorylated version of GFAP remains bound to EEF1A1. When GTP becomes available, EEF1A1 dissociates from GFAP (Bandyopadhyay U et al. 2010). Experiments confirming this binding were performed in rats.

**Preceded by:** p-GFAP binds EEF1A1

**Followed by:** EEF1A1 binds GTP, p-GFAP binds EEF1A1, pGFAP binds GFAP in LAMP2a multimer

### Literature references

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

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## EEF1A1 binds GTP ↗

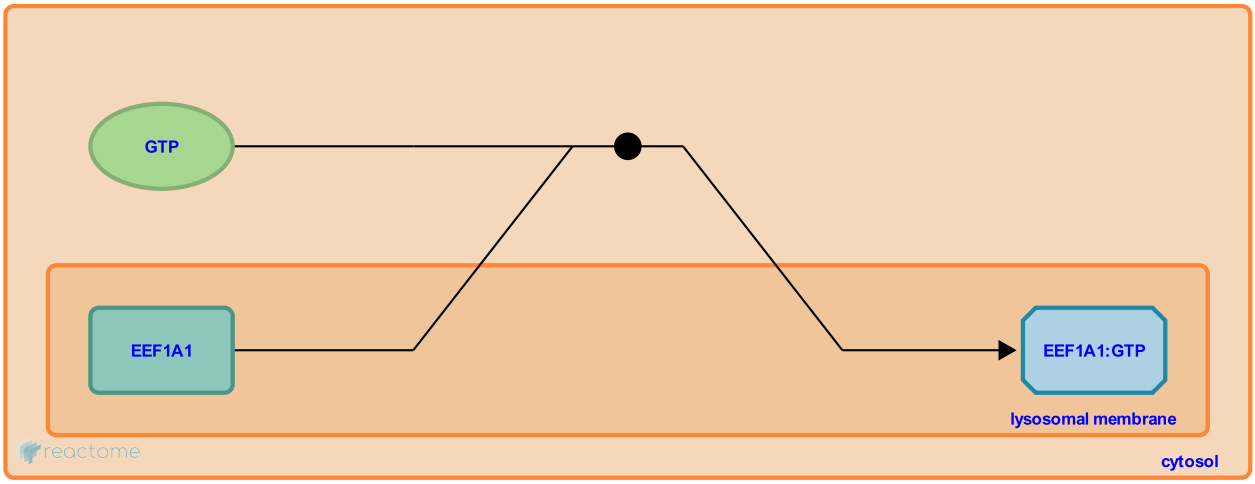
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626038

**Type:** binding

**Compartments:** cytosol, lysosomal membrane

**Inferred from:** Eef1a1 binds GTP (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex stabilized with the aid of HSP90 and glial fibrillary acidic protein (GFAP). This multimer allows the transfer of substrate into the lumen. The stability of this complex is regulated by the dynamics of GFAP and elongation factor 1α (EEF1A1). During autophagy, a phosphorylated version of GFAP remains bound to EEF1A1. When GTP becomes available, Eef1a1 dissociates from GFAP and binds with GTP in the cytosol (Bandyopadhyay U et al. 2010). Experiments confirming this binding were performed in rats.

**Preceded by:** EEF1A1 dissociates from p-GFAP

**Followed by:** EEF1A1:GTP translocates from lysosomal membrane to cytosol

### Literature references

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

### Editions

| | | |
|---|---|---|
| 2019-02-21 | Authored | Varusai, TM. |
| 2019-02-22 | Reviewed | Metzakopian, E. |
| 2019-11-08 | Edited | Varusai, TM. |

## EEF1A1:GTP translocates from lysosomal membrane to cytosol ↗

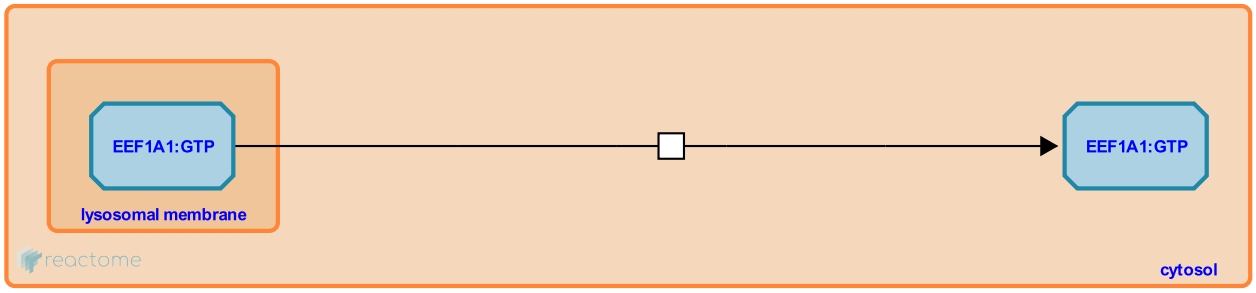
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626067

**Type:** transition

**Compartments:** cytosol, lysosomal membrane

**Inferred from:** Eef1a1:GTP translocates from lysosomal membrane to cytosol (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex stabilized with the aid of HSP90 and glial fibrillary acidic protein (GFAP). This multimer allows the transfer of substrate into the lumen. The stability of this complex is regulated by the dynamics of GFAP and elongation factor 1α (EEF1A1). During autophagy, a phosphorylated version of GFAP remains bound to EEF1A1. When GTP becomes available, EEF1A1 dissociates from GFAP and binds with GTP in the cytosol. Subsequently, EEF1A1 is translocated from lysosomal membrane to cytosol (Bandyopadhyay U et al. 2010). Experiments confirming this binding were performed in rats.

**Preceded by:** EEF1A1 binds GTP

### Literature references

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

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| 2019-02-22 | Reviewed | Metzakopian, E. |
| 2019-11-08 | Edited | Varusai, TM. |

## pGFAP binds GFAP in LAMP2a multimer ↗

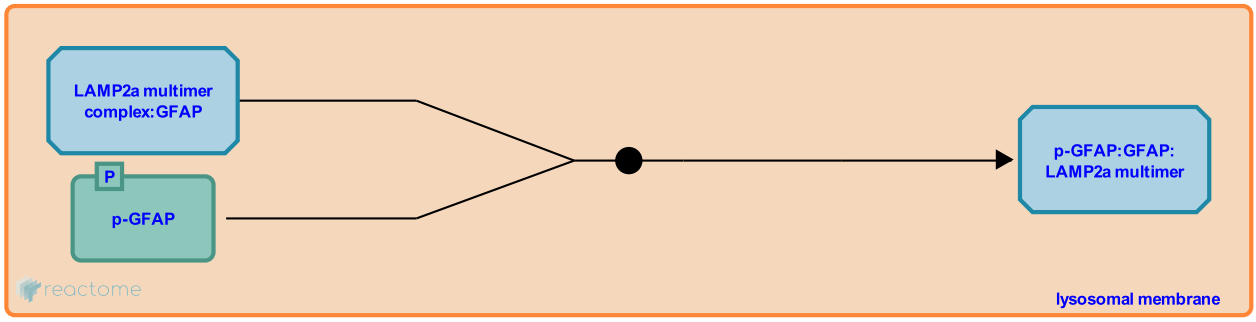
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626039

**Type:** binding

**Compartments:** lysosomal membrane

**Inferred from:** p-Gfap binds Gfap in Lamp2 multimer (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex stabilized with the aid of HSP90 and glial fibrillary acidic protein (GFAP). This multimer allows the transfer of substrate into the lumen. The stability of this complex is regulated by the dynamics of GFAP and elongation factor 1α (EEF1A1). During autophagy, a phosphorylated version of GFAP remains bound to EEF1A1. When GTP becomes available, EEF1A1 dissociates from GFAP and binds with GTP in the cytosol. Subsequently, EEF1A1 is translocated from lysosomal membrane to cytosol. This makes p-GFAP available to bind with GFAP in the LAMP2a multimer complex (Bandyopadhyay U et al. 2010). Experiments confirming this binding were performed in rats.

**Preceded by:** HSPA8:Substrate dissociates from LAMP2a multimer, EEF1A1 dissociates from p-GFAP

**Followed by:** p-GFAP:GFAP dissociates from LAMP2a multimer

### Literature references

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

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## p-GFAP:GFAP dissociates from LAMP2a multimer ↗

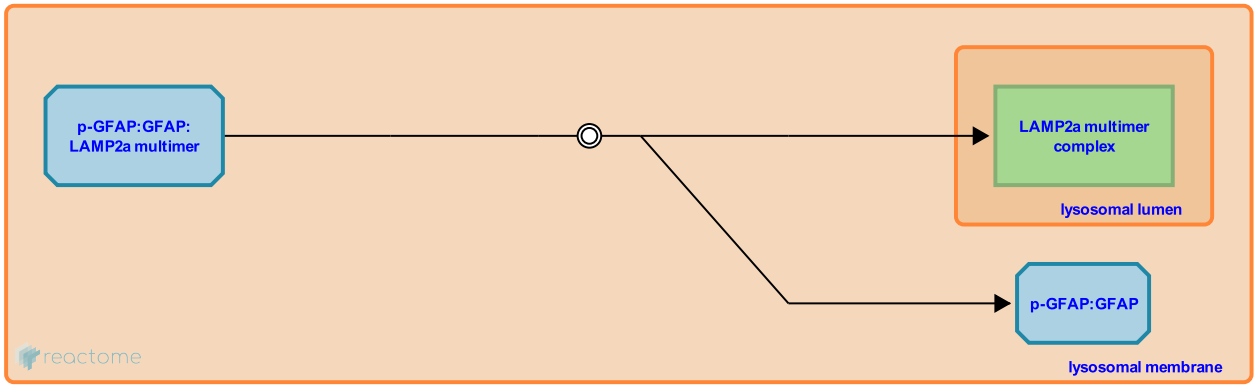
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626242

**Type:** dissociation

**Compartments:** lysosomal membrane

**Inferred from:** p-Gfap:Gfap dissociates from Lamp2 multimer (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex and transfers the substrate into the lumen. The stability of this complex is regulated by the dynamics of glial fibrillary acidic protein (GFAP) and elongation factor 1α (EEF1A1). During autophagy, a phosphorylated version of GFAP remains bound to EEF1A1. When GTP becomes available, EEF1A1 dissociates from GFAP and binds with GTP in the cytosol. This makes p-GFAP available to bind with GFAP in the LAMP2a multimer complex. Consequently, p-GFAP sequesters GFAP from LAMP2a multimer (Bandyopadhyay U et al. 2010). Experiments confirming this event were performed in rats.

**Preceded by:** pGFAP binds GFAP in LAMP2a multimer

**Followed by:** HSPA8 binds LAMP2a multimers

### Literature references

Bandyopadhyay, U., Sridhar, S., Kaushik, S., Kiffin, R., Cuervo, AM. (2010). Identification of regulators of chaperone-mediated autophagy. *Mol. Cell, 39*, 535-47. ↗

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| 2019-11-08 | Edited | Varusai, TM. |

## HSPA8 binds LAMP2a multimers ↗

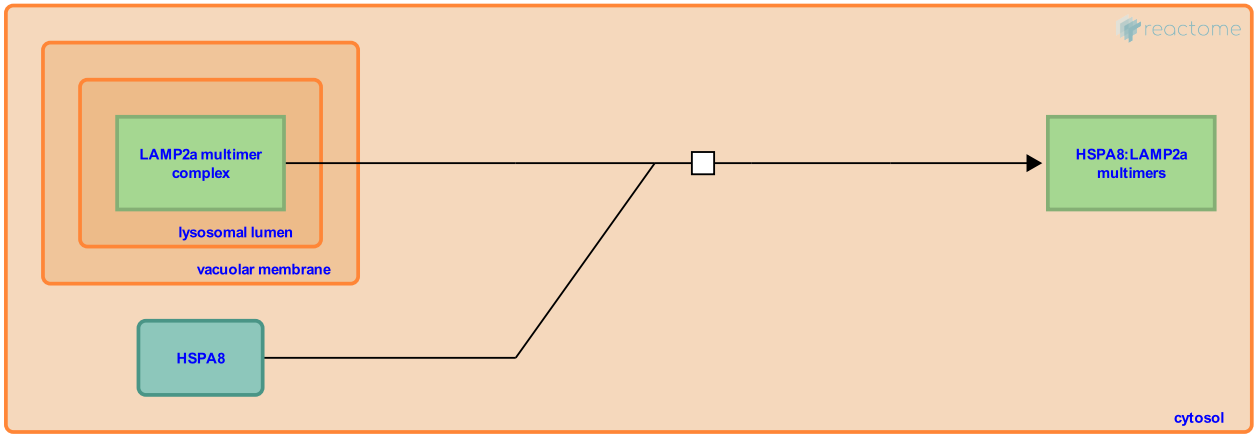
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626253

**Type:** transition

**Compartments:** cytosol, lysosomal membrane

**Inferred from:** Hspa8 binds Lamp2 multimers (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex and transfers the substrate into the lumen. The stability of this complex is regulated by the dynamics of HSPA8. Cytosolic HSPA8 binds with LAMP2a multimers in the lysosomal membrane and triggers their disassembly. Interestingly, substrate bound HSPA8 do not have this effect on LAMP2a (Bandyopadhyay U et al. 2008). Experiments confirming this event were performed in rats.

**Preceded by:** p-GFAP:GFAP dissociates from LAMP2a multimer, HSPA8 dissociates from LAMP2a, HSPA8 dissociates from LAMP2A-bound substrate

**Followed by:** HSPA8:LAMP2a multimers depolymerizes to monomers

### Literature references

Bandyopadhyay, U., Kaushik, S., Varticovski, L., Cuervo, AM. (2008). The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell. Biol., 28*, 5747-63. ↗

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## HSPA8:LAMP2a multimers depolymerizes to monomers ↗

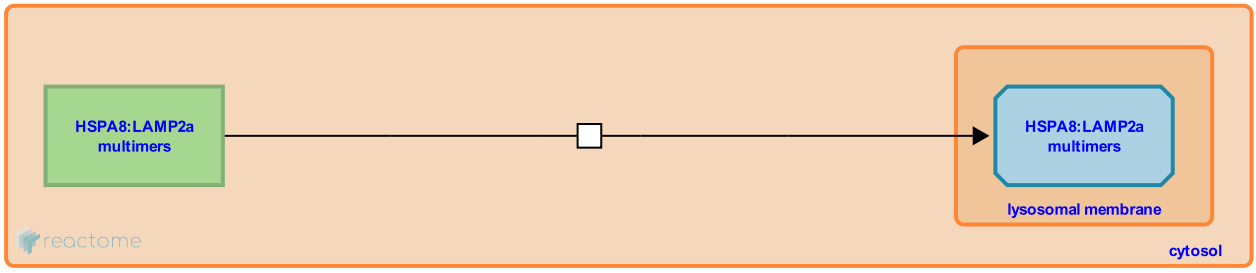
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626256

**Type:** transition

**Compartments:** cytosol, lysosomal membrane

**Inferred from:** Hspa8:Lamp2 multimers depolymerizes to monomers (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex and transfers the substrate into the lumen. The stability of this complex is regulated by the dynamics of HSPA8. Cytosolic HSPA8 binds with LAMP2a multimers in the lysosomal membrane. This triggers the disassembly of multimeric complexes into monomeric units (Bandyopadhyay U et al. 2008). Experiments confirming this event were performed in rats.

**Preceded by:** HSPA8 binds LAMP2a multimers

**Followed by:** HSPA8 dissociates from LAMP2a

### Literature references

Bandyopadhyay, U., Kaushik, S., Varticovski, L., Cuervo, AM. (2008). The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell. Biol., 28*, 5747-63. ↗

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## HSPA8 dissociates from LAMP2a ↗

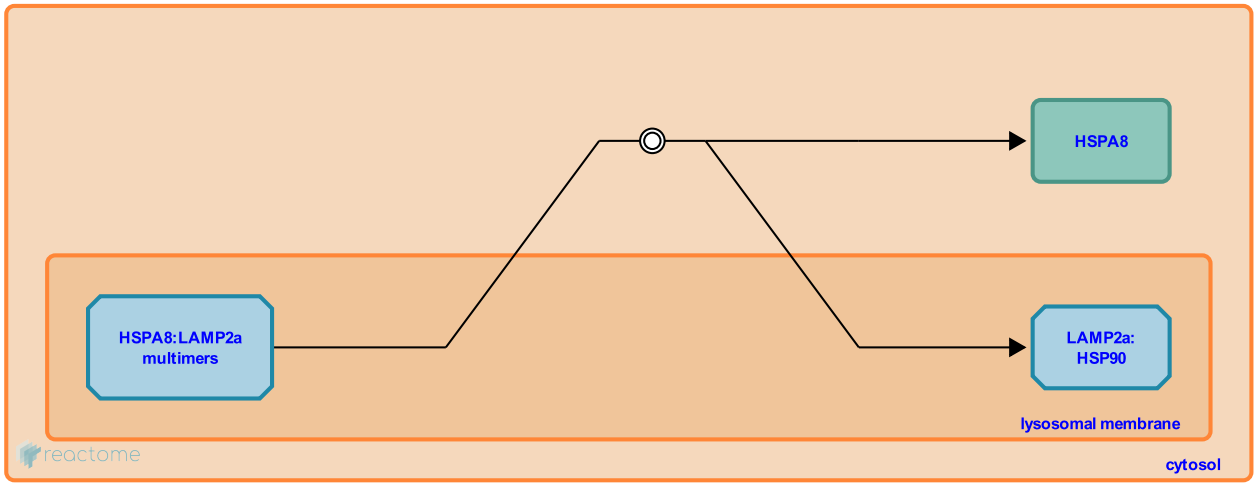
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626235

**Type:** dissociation

**Compartments:** cytosol, lysosomal membrane

**Inferred from:** Hspa8 dissociates from Lamp2 (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex and transfers the substrate into the lumen. The stability of this complex is regulated by the dynamics of HSPA8. Cytosolic HSPA8 binds with LAMP2a multimers in the lysosomal membrane and triggers their disassembly into monomeric units (Bandyopadhyay U et al. 2008). HSPA8 dissociates from LAMP2a to make it available for further substrate autophagy. Experiments related to this event were performed in rats.

**Preceded by:** HSPA8:LAMP2a multimers depolymerizes to monomers

**Followed by:** HSP90 dissociates from LAMP2a, HSPA8 binds LAMP2a multimers, HSPA8 binds substrate

### Literature references

Bandyopadhyay, U., Kaushik, S., Varticovski, L., Cuervo, AM. (2008). The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell. Biol., 28*, 5747-63. ↗

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## HSP90 dissociates from LAMP2a

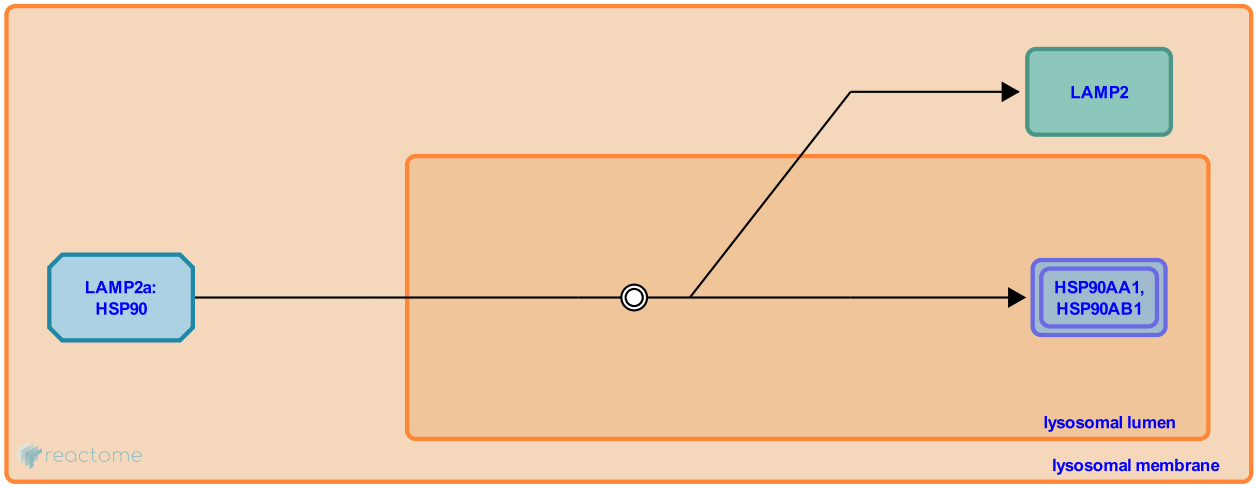
**Location:** Chaperone Mediated Autophagy

**Stable identifier:** R-HSA-9626276

**Type:** dissociation

**Compartments:** lysosomal lumen, lysosomal membrane

**Inferred from:** Hsp90 dissociates from Lamp2 (Rattus norvegicus)




Intracellular proteins are targeted for proteolytic degradation in lysosome with the aid of chaperones. Heat shock cognate 71 kDa protein (HSPA8) transports substrates from the cytosol to the lysosomal membrane where it binds to Lysosome-associated membrane glycoprotein 2 (LAMP2a). Subsequently, LAMP2a forms a multimeric complex and transfers the substrate into the lumen. The stability of this complex is regulated by the dynamics of Heat shock protein HSP 90 (HSP90) and HSPA8 (Bandyopadhyay U et al. 2008). HSPA8 and HSP90 dissociate from LAMP2a to make it available for further substrate autophagy. Experiments related to this event were performed in rats.

**Preceded by:** HSPA8 dissociates from LAMP2a

**Followed by:** HSPA8:Substrate binds LAMP2a, Substrate:LAMP2a binds HSP90

## Literature references

Bandyopadhyay, U., Kaushik, S., Varticovski, L., Cuervo, AM. (2008). The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell. Biol., 28*, 5747-63.

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