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


Reactome database release: 82

This document contains 1 pathway and 19 reactions (see Table of Contents)
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


Editions

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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-bound substrate, HSPA8 dissociates from LAMP2a

Followed by: HSPA8:Substrate binds LAMP2a

Literature references


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**


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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: HSPA8 binds LAMP2a multimers, Substrate:LAMP2a binds HSP90, HSPA8 binds substrate

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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

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

**Followed by:** GFAP binds LAMP2a multimer

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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

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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

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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**


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**


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


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

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

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

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**Preceded by:** EEF1A1 binds GTP

**Literature references**

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

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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

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

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

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

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

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

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**Preceded by:** HSPA8 dissociates from LAMP2a

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

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Introduction

Chaperone Mediated Autophagy

- HSPA8 binds substrate
- HSPA8:Substrate binds LAMP2a
- HSPA8 dissociates from LAMP2A-bound substrate
- Substrate:LAMP2a binds HSP90
- Substrate:LAMP2a:HSP90 polymerizes
- GFAP binds LAMP2a multimer
- Unfolded substrate in LAMP2a multimeric complex binds HSPA8
- HSPA8 transports unfolded substrate to lysosomal lumen for degradation
- HSPA8:Substrate dissociates from LAMP2a multimer
- p-GFAP binds EEF1A1
- EEF1A1 dissociates from p-GFAP
- EEF1A1 binds GTP
- EEF1A1:GTP translocates from lysosomal membrane to cytosol
- pGFAP binds GFAP in LAMP2a multimer
- p-GFAP:GFAP dissociates from LAMP2a multimer
- HSPA8 binds LAMP2a multimers
- HSPA8:LAMP2a multimers depolymerizes to monomers
- HSPA8 dissociates from LAMP2a
- HSP90 dissociates from LAMP2a

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