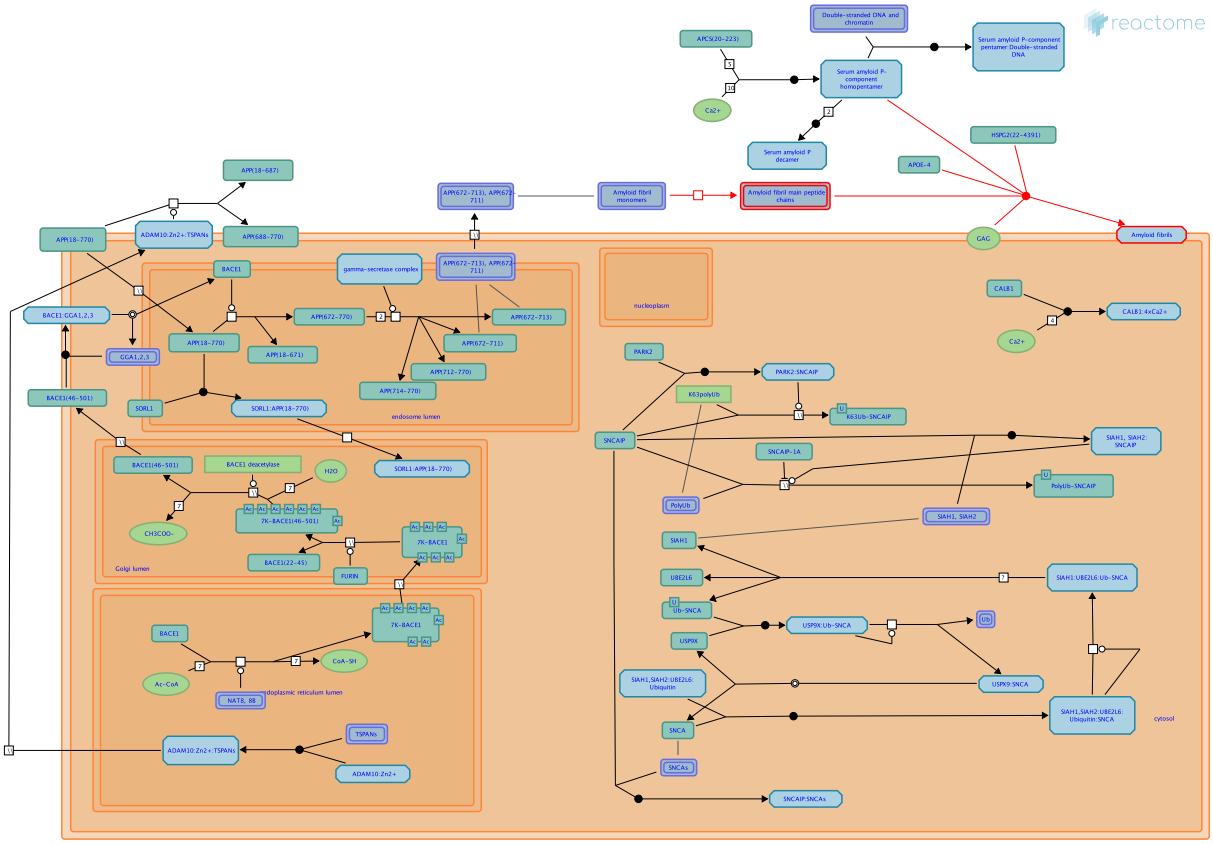
Amyloid fiber formation



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14/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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. ↗

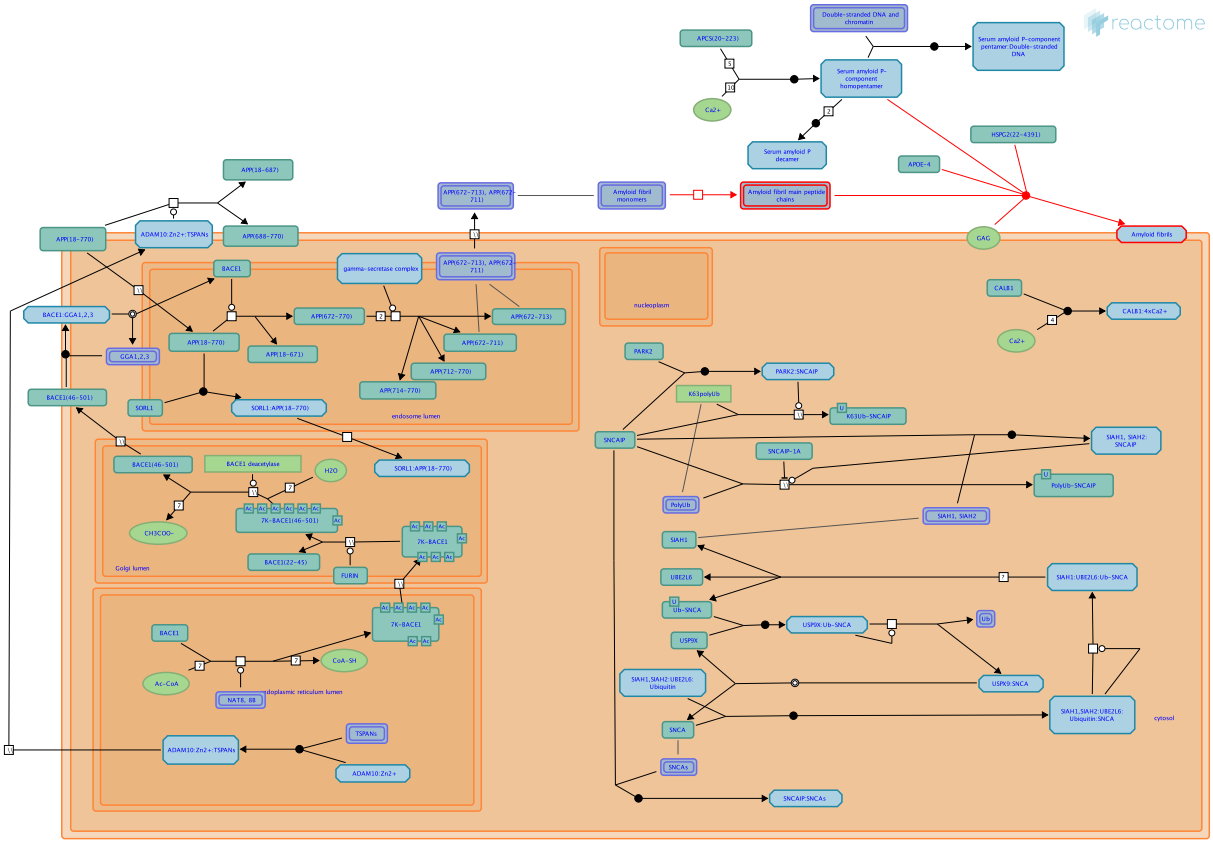
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Amyloid fiber formation ↗

Stable identifier: R-HSA-977225



Amyloid is a term used to describe deposits of fibrillar proteins, typically extracellular. The abnormal accumulation of amyloid, amyloidosis, is a term associated with tissue damage caused by amyloid deposition, seen in numerous diseases including neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's. Amyloid deposits consist predominantly of amyloid fibrils, rigid, non-branching structures that form ordered assemblies, characteristically with a cross beta-sheet structure where the sheets run parallel to the direction of the fibril (Sawaya et al. 2007). Often the fibril has a left-handed twist (Nelson & Eisenberg 2006). At least 27 human proteins form amyloid fibrils (Sipe et al. 2010). Many of these proteins have non-pathological functions; the trigger that leads to abnormal aggregations differs between proteins and is not well understood but in many cases the peptides are abnormal fragments or mutant forms arising from polymorphisms, suggesting that the initial event may be aggregation of misfolded or unfolded peptides. Early studies of Amyloid-beta assembly led to a widely accepted model that assembly was a nucleation-dependent polymerization reaction (Teplow 1998) but it is now understood to be more complex, with multiple 'off-pathway' events leading to a variety of oligomeric structures in addition to fibrils (Roychaudhuri et al. 2008), though it is unclear whether these intermediate steps are required in vivo. An increasing body of evidence suggests that these oligomeric forms are primarily responsible for the neurotoxic effects of Amyloid-beta (Roychaudhuri et al. 2008), alpha-synuclein (Winner et al. 2011) and tau (Dance & Strobel 2009, Meraz-Rios et al. 2010). Amyloid oligomers are believed to have a common structural motif that is independent of the protein involved and not present in fibrils (Kayed et al. 2003). Conformation dependent, aggregation specific antibodies suggest that there are 3 general classes of amyloid oligomer structures (Glabe 2009) including annular structures which may be responsible for the widely reported membrane permeabilization effect of amyloid oligomers. Toxicity of amyloid oligomers preceeds the appearance of plaques in mouse models (Ferretti et al. 2011).

Fibrils are often associated with other molecules, notably heparan sulfate proteoglycans and Serum

Amyloid P-component, which are universally associated and seem to stabilize fibrils, possibly by protecting them from degradation.

Literature references

Westermark, P. (2005). Aspects on human amyloid forms and their fibril polypeptides. *FEBS J, 272*, 5942-9. ↗

Editions

2010-10-15	Authored	Jupe, S.
2011-04-08	Edited	Jupe, S.
2011-04-08	Reviewed	Perry, G.
2015-11-09	Reviewed	Perry, G.

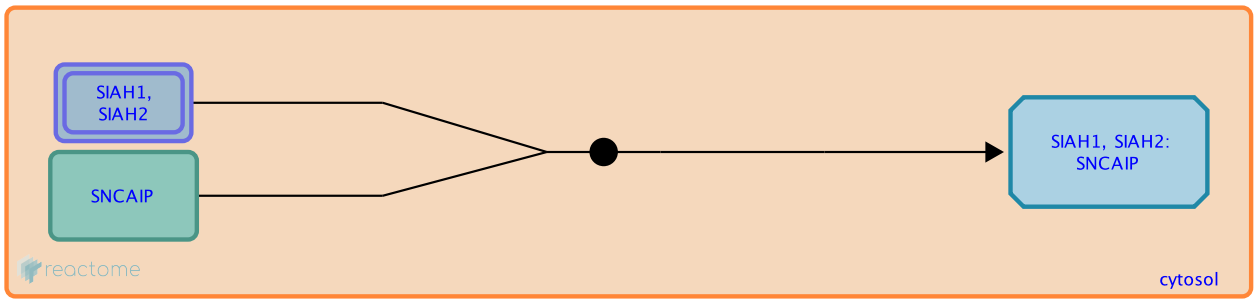
SIAH1, SIAH2 bind SNCAIP ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5658092

Type: binding

Compartments: cytosol



Seven in absentia homolog 1 (SIAH1) and 2 (SIAH2) are E3 ubiquitin-protein ligases that mediate ubiquitination of a number of target proteins including Synphilin-1 (SNCAIP) (Nagano et al. 2003) and alpha-synuclein (Liani et al. 2004). They are inhibited by the 1A isoform of SNCAIP (Szargel et al. 2009). When ubiquitinated by SIAH1, SNCAIP is targetted for proteasomal degradation (Nagano et al. 2003).

Synphilin-1 (SNCAIP) is a presynaptic protein that associates with synaptic vesicles (Ribeiro et al. 2002). It is present in many types of cytoplasmic inclusions, where it colocalizes with alpha-synuclein. It is associated with Parkinson's Disease (PD) because it is an intrinsic component of Lewy bodies (Wakabayashi et al. 2000) and a mutation of the SNCAIP gene has been identified in some PD patients (Marx et al. 2003), suggesting that accumulation of synphilin-1 and its interaction with alpha-synuclein may be relevant for Lewy body formation in PD.

Synphilin-1 (SNCAIP) is ubiquitinated by several other E3 ubiquitin-ligases, including Parkin (Chung et al. 2001) and Dorfin (Ito et al. 2003).

Followed by: SIAH1, SIAH2 ubiquitinate SNCAIP

Literature references

Nagano, Y., Yamashita, H., Takahashi, T., Kishida, S., Nakamura, T., Iseki, E. et al. (2003). Siah-1 facilitates ubiquitination and degradation of synphilin-1. *J. Biol. Chem., 278*, 51504-14. ↗

Liani, E., Eyal, A., Avraham, E., Shemer, R., Szargel, R., Berg, D. et al. (2004). Ubiquitylation of synphilin-1 and alpha-synuclein by SIAH and its presence in cellular inclusions and Lewy bodies imply a role in Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A., 101*, 5500-5. ↗

Editions

2014-12-17	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

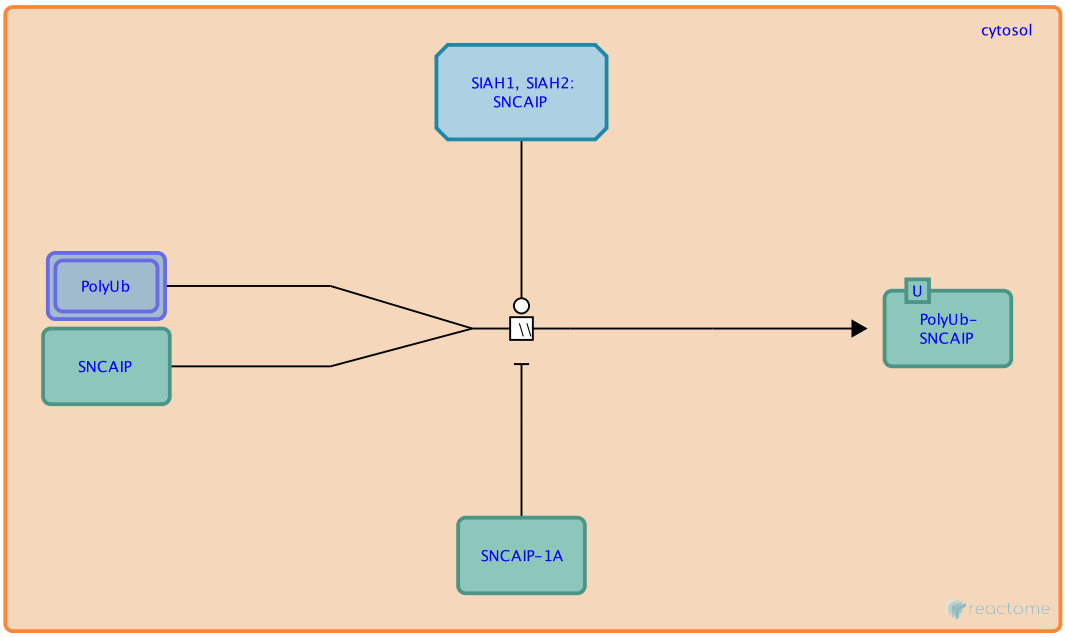
SIAH1, SIAH2 ubiquitinate SNCAIP ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5667107

Type: omitted

Compartments: cytosol



Seven in absentia homolog (SIAH1) and 2 (SIAH2) are E3 ubiquitin-protein ligases that mediate ubiquitination of a number of target proteins including Synphilin-1 (SNCAIP) (Nagano et al. 2003, Liani et al. 2004). When ubiquitinated by SIAH1, SNCAIP is targetted for proteasomal degradation (Nagano et al. 2003). SIAH1 and SIAH2 are inhibited by the 1A isoform of SNCAIP (Szargel et al. 2009). SIAH1 can bind the brain-enriched E2 ubiquitin-conjugating enzyme UBE2L6 (Lee et al. 2008) but the E2 involved in SNCAIP ubiquitination has not been established.

Synphilin-1 (SNCAIP) is a presynaptic protein that associates with synaptic vesicles (Ribeiro et al. 2002). It is present in many types of cytoplasmic inclusions, where it colocalizes with alpha-synuclein. It is associated with Parkinson's Disease (PD) because it is an intrinsic component of Lewy bodies (Wakabayashi et al. 2000) and a mutation of the SNCAIP gene has been identified in some PD patients (Marx et al. 2003), suggesting that accumulation of synphilin-1 and its interaction with alpha-synuclein may be relevant for Lewy body formation in PD.

Synphilin-1 (SNCAIP) is ubiquitinated by several other E3 ubiquitin-ligases, including Parkin (Chung et al. 2001) and Dorfin (Ito et al. 2003).

Preceded by: SIAH1, SIAH2 bind SNCAIP

Literature references

Nagano, Y., Yamashita, H., Takahashi, T., Kishida, S., Nakamura, T., Iseki, E. et al. (2003). Siah-1 facilitates ubiquitination and degradation of synphilin-1. *J. Biol. Chem., 278*, 51504-14. ↗

Liani, E., Eyal, A., Avraham, E., Shemer, R., Szargel, R., Berg, D. et al. (2004). Ubiquitylation of synphilin-1 and alpha-synuclein by SIAH and its presence in cellular inclusions and Lewy bodies imply a role in Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A., 101*, 5500-5. ↗

Editions

2015-01-23	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

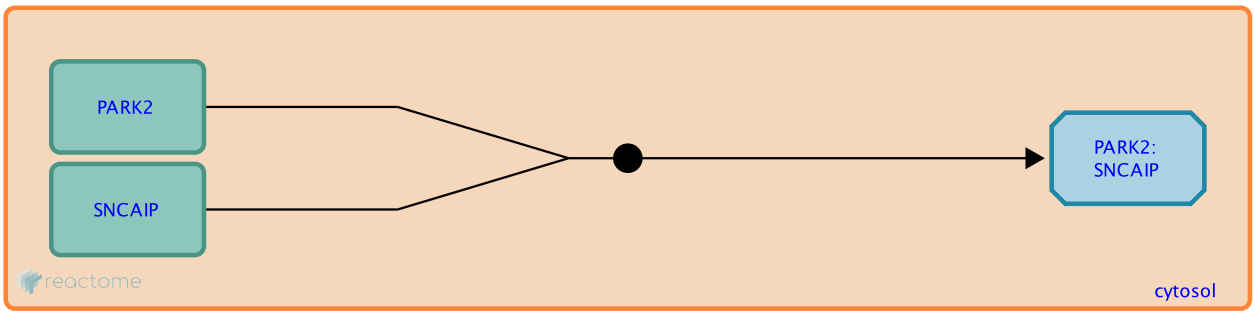
PARK2 binds SNCAIP ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5658574

Type: binding

Compartments: cytosol



Synphilin-1 (SNCAIP) is a presynaptic protein that associates with synaptic vesicles (Ribeiro et al. 2002). It is present in many types of cytoplasmic inclusions, where it colocalizes with alpha-synuclein (SNCA). It is associated with Parkinson's Disease (PD) because it is an intrinsic component of Lewy bodies (Wakabayashi et al. 2000) and a mutation of the SNCAIP gene has been identified in some PD patients (Marx et al. 2003), suggesting that accumulation of SNCAIP and its interaction with SNCA may be relevant for Lewy body formation in PD.

SNCAIP is ubiquitinated by several different E3 ubiquitin-ligases, including Parkin (PARK2). PARK2 over-expression with SNCAIP in cell culture leads to the formation of protein aggregates (Chung et al. 2001). PARK2 preferentially mediates the addition of lysine-63 (K63)-linked polyubiquitination of SNCAIP (Lim et al. 2005). This leads to SNCAIP degradation only at an unusually high PARK2 to SNCAIP ratio (Lim et al. 2005). K63-linked ubiquitination may be a signal that leads to the degradation of inclusions by autophagy when the ubiquitin-proteasome system is dysfunctional (Lin et al. 2005, Tan et al. 2008).

Literature references

Chung, KK., Zhang, Y., Lim, KL., Tanaka, Y., Huang, H., Gao, J. et al. (2001). Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. *Nat. Med., 7*, 1144-50. ↗

Editions

2014-12-19	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

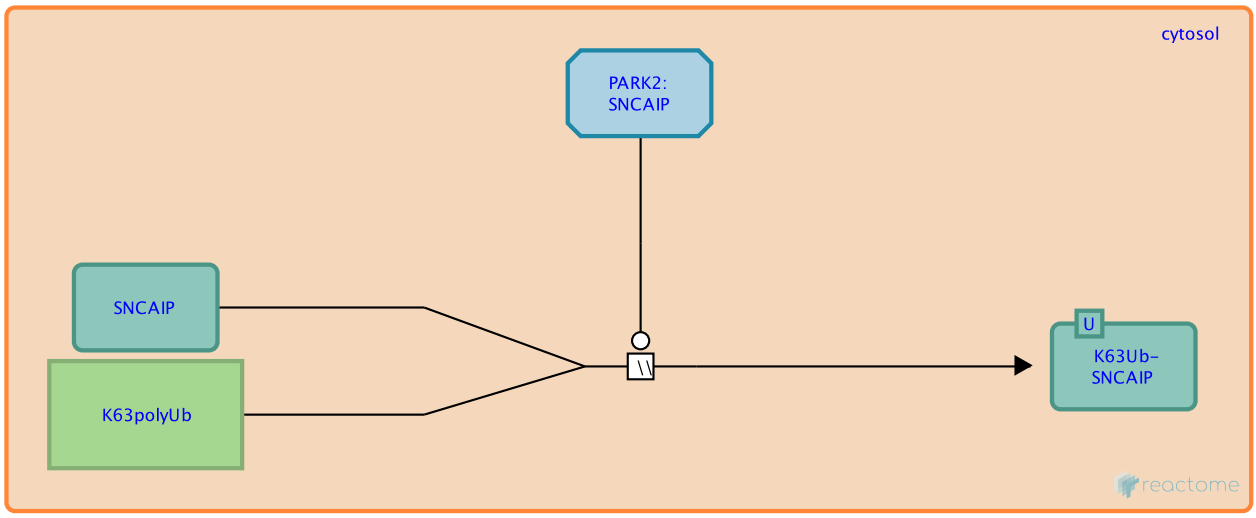
PARK2 K63-Ubiquitinates SNCAIP ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5667111

Type: omitted

Compartments: cytosol



SNCAIP is ubiquitinated by several different E3 ubiquitin-ligases, including Parkin (PARK2). PARK2 over-expression with SNCAIP in cell culture leads to the formation of protein aggregates (Chung et al. 2001). PARK2 preferentially mediates the addition of lysine-63 (K63)-linked polyubiquitination of SNCAIP (Lim et al. 2005). This leads to SNCAIP degradation only at an unusually high PARK2 to SNCAIP ratio (Lim et al. 2005). K63-linked ubiquitination may be a signal that leads to the degradation of inclusions by autophagy when the ubiquitin-proteasome system is dysfunctional (Lim et al. 2005, Tan et al. 2008).

Literature references

Chung, KK., Zhang, Y., Lim, KL., Tanaka, Y., Huang, H., Gao, J. et al. (2001). Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. *Nat. Med., 7*, 1144-50. ↗

Editions

2015-01-23	Authored	Jupe, S.
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2015-11-09	Reviewed	Perry, G.

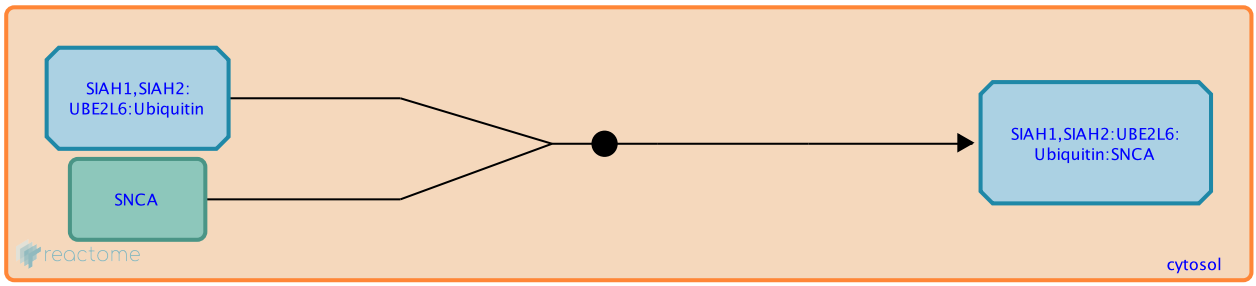
SIAH1:UBE2L6:Ubiquitin binds SNCA

Location: Amyloid fiber formation

Stable identifier: R-HSA-5658496

Type: binding

Compartments: cytosol



Seven in absentia homolog 1 (SIAH1) and 2 (SIAH2) are E3 ubiquitin-protein ligases that mediates ubiquitination of a number of target proteins including Synphilin-1 (SNCAIP) (Nagano et al. 2003) and alpha-synuclein (SNCA) (Liani et al. 2004, Lee et al. 2008). Ubiquitination of SNCA by SIAH1 is disrupted by the Parkinson's Disease (PD)-linked A30P mutation but not by the A53T mutation. SIAH1 binds the E2 ubiquitin-conjugating enzyme UBE2L6 (UBCH8) (Lee et al. 2008). This facilitates the mono- and di-ubiquitination of SNCA in vivo, but does not target SNCA for proteasomal degradation, rather it promotes SNCA aggregation and enhances toxicity (Lee et al. 2008). Monoubiquitinated SNCA may work as a seed for aggregation (Engelender 2008) and recruit other PD-related proteins, such as SNCAIP and UCHL1.

Followed by: SIAH1:UBE2L6:Ubiquitin ubiquitinates SNCA

Literature references

Lee, JT., Wheeler, TC., Li, L., Chin, LS. (2008). Ubiquitination of alpha-synuclein by Siah-1 promotes alpha-synuclein aggregation and apoptotic cell death. *Hum. Mol. Genet., 17*, 906-17.

Editions

2014-12-19	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

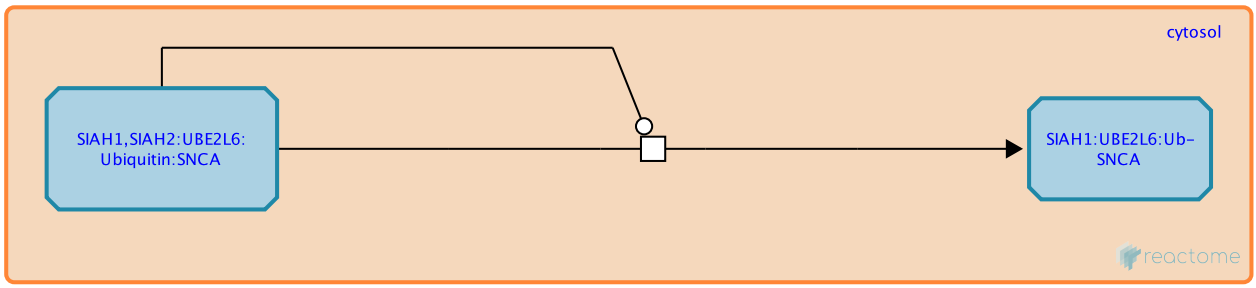
SIAH1:UBE2L6:Ubiquitin ubiquitinates SNCA ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5660753

Type: transition

Compartments: cytosol



SIAH1 transfers ubiquitin from UBE2L6 to SNCA, generating monoubiquitinated SNCA (Ub-SNCA) (Liani et al 2004, Rott et al. 2008, Lee et al. 2008). Monoubiquitination of SNCA promotes its aggregation in vitro and in vivo, which is toxic to cells. Lewy Bodies, a characteristic of Parkinson's Disease, contain monoubiquitinted SNCA deposits (Hasegawa et al. 2002). Mass spectrometry analysis demonstrates that SIAH monoubiquitinates alpha-synuclein at lysines 12, 21, and 23 (Rott et al. 2008).

Monoubiquitination is generally thought to lead to degradation via the lysosomal pathway (d'Azzo et al. 2005) but monoubiquitinated SNCA appears to be preferentially targeted for degradation by the proteasome (Rott et al. 2011).

Preceded by: SIAH1:UBE2L6:Ubiquitin binds SNCA

Followed by: Ub-SNCA dissociates from the conjugating enzyme

Literature references

Rott, R., Szargel, R., Haskin, J., Shani, V., Shainskaya, A., Manov, I. et al. (2008). Monoubiquitylation of alpha-synuclein by seven in absentia homolog (SIAH) promotes its aggregation in dopaminergic cells. *J. Biol. Chem., 283,* 3316-28. ↗

Editions

2015-01-06	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

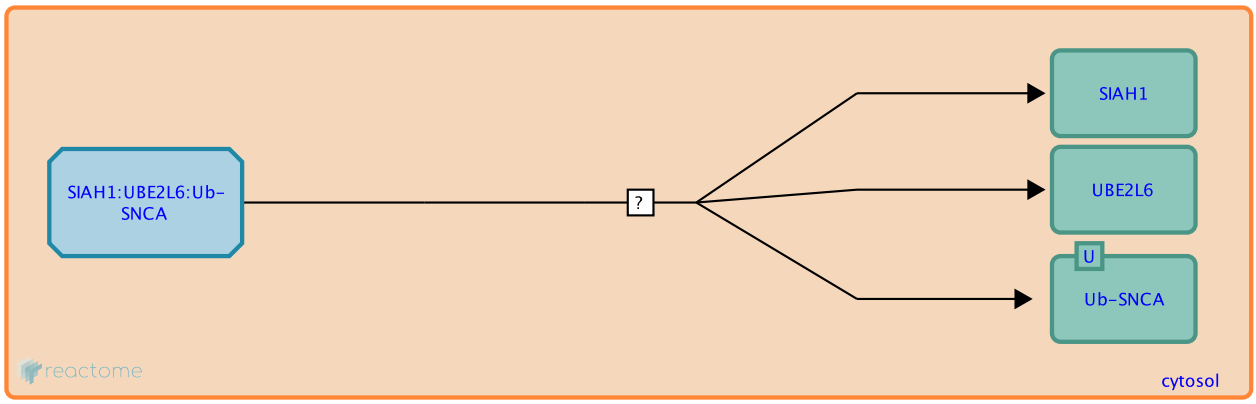
Ub-SNCA dissociates from the conjugating enzyme ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5660757

Type: uncertain

Compartments: cytosol



SNCA is monoubiquitinated and under some circumstances released to accumulate in the cell. Alternatively Ub-SNCA may undergo further rounds of ubiquitination producing diubiquitinated or polyubiquitinated forms. The precise mechanism of release and subsequent further ubiquitination is unclear (Sadowski et al. 2011); the E3 ligase may remain bound to SNCA while the E2 ligase dissociates to be replaced by a Ubiquitin-associated replacement, or the E2/E3 complex may dissociate completely allowing a different E3 to bind the SNCA substrate.

Preceded by: SIAH1:UBE2L6:Ubiquitin ubiquitinates SNCA

Followed by: USP9X binds Ub-SNCA

Literature references

Rott, R., Szargel, R., Haskin, J., Shani, V., Shainskaya, A., Manov, I. et al. (2008). Monoubiquitylation of alpha-synuclein by seven in absentia homolog (SIAH) promotes its aggregation in dopaminergic cells. *J. Biol. Chem., 283*, 3316-28. ↗

Sadowski, M., Suryadinata, R., Tan, AR., Roesley, SN., Sarcevic, B. (2012). Protein monoubiquitination and polyubiquitination generate structural diversity to control distinct biological processes. *IUBMB Life, 64*, 136-42. ↗

Editions

2015-01-06	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

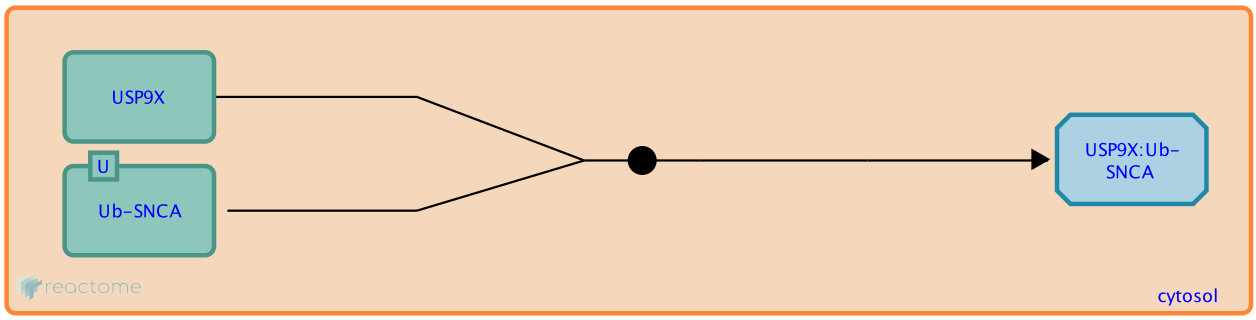
USP9X binds Ub-SNCA ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5661157

Type: binding

Compartments: cytosol



The deubiquitinase USP9X binds and deubiquitinates alpha-synuclein (SNCA) in vitro and in vivo, showing co-accumulation with SNCA in Lewy Bodies. Knockdown of USP9X expression in conditions of proteolytic inhibition leads to the accumulation of monoubiquitinated SNCA and increases the aggregation of SNCA into toxic inclusions, strengthening the connection between monoubiquitination, inclusion formation, and toxicity of SNCA. USP9X cytosolic levels are lower in Diffuse Lewy Body disease and Parkinson's Disease tissues, which may contribute to the accumulation and aggregation of monoubiquitinated SNCA (Rott et al. 2011).

Preceded by: Ub-SNCA dissociates from the conjugating enzyme

Followed by: USP9X deubiquitinates Ub-SNCA

Literature references

Rott, R., Szargel, R., Haskin, J., Bandopadhyay, R., Lees, AJ., Shani, V. et al. (2011). ?-Synuclein fate is determined by USP9X-regulated monoubiquitination. *Proc. Natl. Acad. Sci. U.S.A., 108*, 18666-71. ↗

Editions

2015-01-09	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

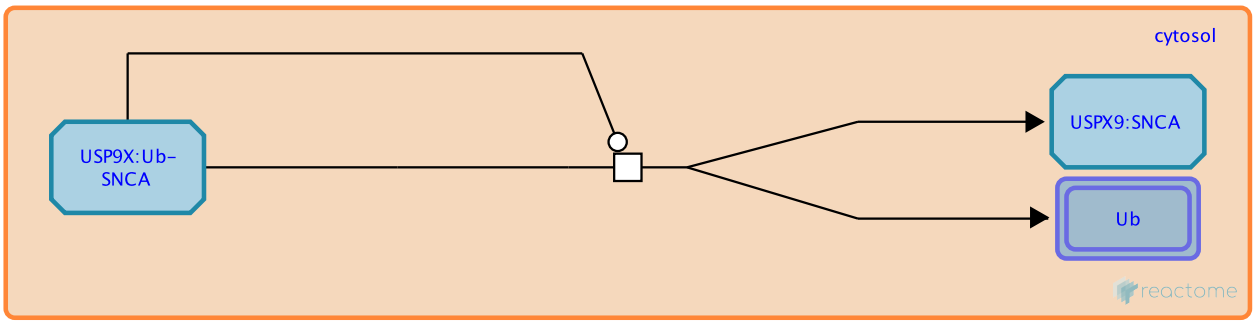
USP9X deubiquitinates Ub-SNCA ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5660752

Type: transition

Compartments: cytosol



The deubiquitinase USP9X binds and deubiquitinates alpha-synuclein (SNCA) in vitro and in vivo, showing co-accumulation with SNCA in Lewy Bodies. Knockdown of USP9X expression in conditions of proteolytic inhibition leads to the accumulation of monoubiquitinated SNCA and increases the aggregation of SNCA into toxic inclusions, strengthening the connection between monoubiquitination, inclusion formation, and toxicity of SNCA. USP9X cytosolic levels are lower in Diffuse Lewy Body disease and Parkinson's Disease tissues, which may contribute to the accumulation and aggregation of monoubiquitinated SNCA (Rott et al. 2011).

Preceded by: USP9X binds Ub-SNCA

Literature references

Rott, R., Szargel, R., Haskin, J., Bandopadhyay, R., Lees, AJ., Shani, V. et al. (2011). ?-Synuclein fate is determined by USP9X-regulated monoubiquitination. *Proc. Natl. Acad. Sci. U.S.A., 108*, 18666-71. ↗

Editions

2015-01-06	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

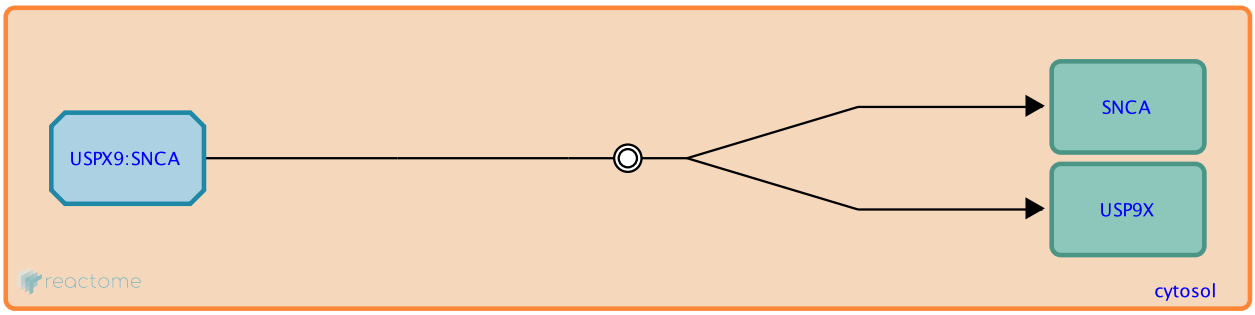
USP9X:SNCA dissociates ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5661161

Type: dissociation

Compartments: cytosol



Following the removal of ubiquitin, SNCA is released by USP9X (Rott et al. 2011).

Literature references

Rott, R., Szargel, R., Haskin, J., Bandopadhyay, R., Lees, AJ., Shani, V. et al. (2011). ?-Synuclein fate is determined by USP9X-regulated monoubiquitination. *Proc. Natl. Acad. Sci. U.S.A., 108*, 18666-71. ↗

Sadowski, M., Suryadinata, R., Tan, AR., Roesley, SN., Sarcevic, B. (2012). Protein monoubiquitination and polyubiquitination generate structural diversity to control distinct biological processes. *IUBMB Life, 64*, 136-42. ↗

Editions

2015-01-09	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

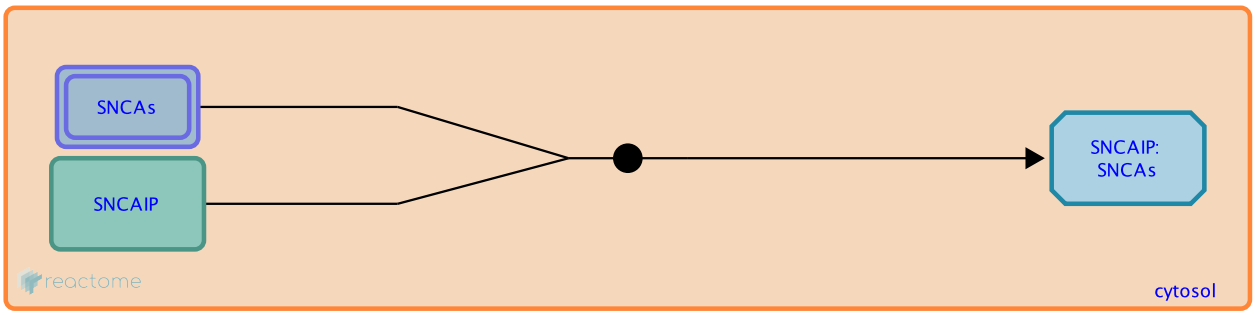
SNCAIP binds alpha-synuclein ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5658104

Type: binding

Compartments: cytosol



Synphilin-1 (SNCAIP) binds alpha-synuclein (SNCAs) in vivo, which promotes the formation of Lewy body-like inclusions that are characteristic of Parkinson's Disease (Engelender et al. 1999, Kawamata et al. 2001). SNCAIP and PARK2 (Parkin) are found in the central core of a majority of Lewy Bodies in Parkinson's disease (Bandopadhyay et al. 2005).

Literature references

Engelender, S., Kaminsky, Z., Guo, X., Sharp, AH., Amaravi, RK., Kleiderlein, JJ. et al. (1999). Synphilin-1 associates with alpha-synuclein and promotes the formation of cytosolic inclusions. *Nat. Genet., 22*, 110-4. ↗

Editions

2014-12-17	Authored	Jupe, S.
2015-11-04	Edited	Jupe, S.
2015-11-09	Reviewed	Perry, G.

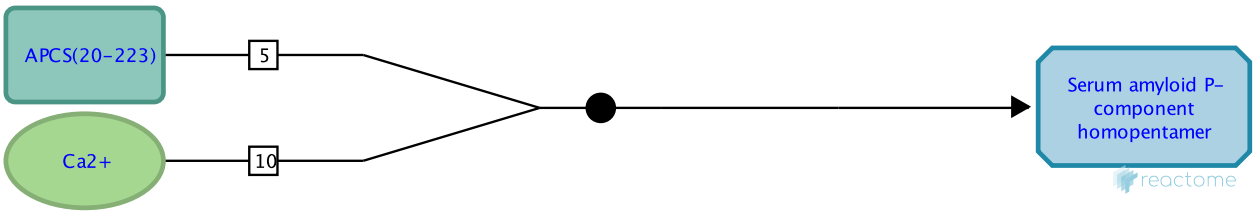
Serum amyloid P-component forms homopentamers ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-976723

Type: binding

Compartments: extracellular region



Serum amyloid P component (SAP) is a member of the pentraxin family, characterized by the formation of pentameric ring structures. Each member of the ring has two associated calcium ions. SAP is an acute phase reactant, highly induced by IL-6. It has 50% homology with the related C-reactive peptide.

Followed by: Formation of serum amyloid P decamer, Amyloid fibrils have additional components, Serum amyloid P binds DNA and chromatin

Literature references

Emsley, J., White, HE., O'Hara, BP., Oliva, G., Srinivasan, N., Tickle, IJ. et al. (1994). Structure of pentameric human serum amyloid P component. *Nature, 367*, 338-45. ↗

Editions

2010-10-15	Authored	Jupe, S.
2011-04-08	Edited	Jupe, S.
2011-04-08	Reviewed	Perry, G.
2015-11-09	Reviewed	Perry, G.

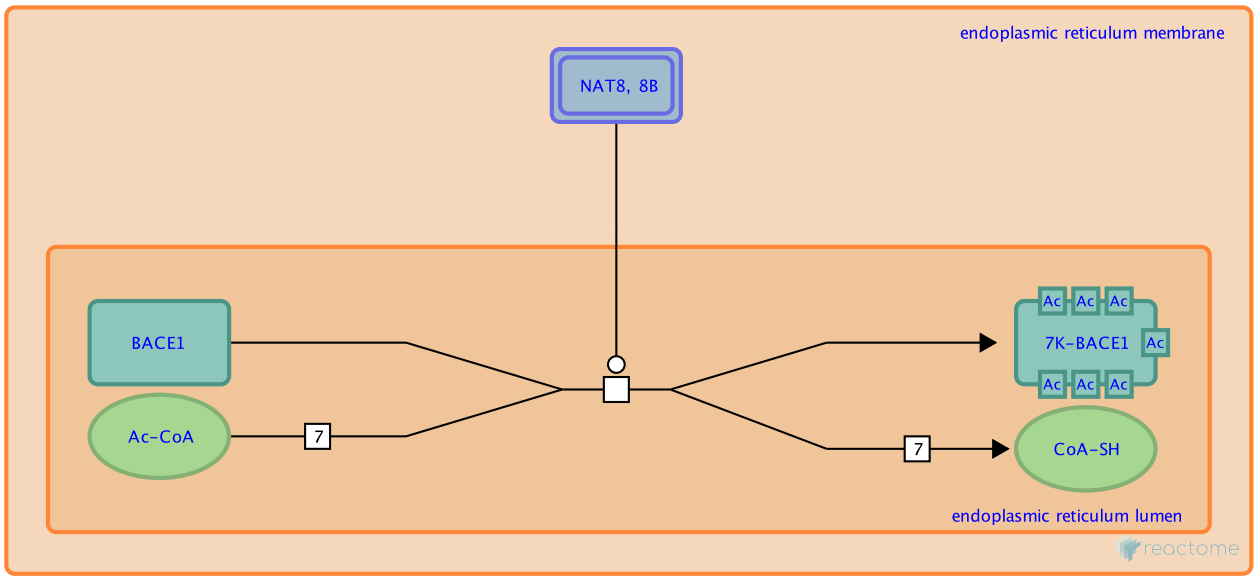
NAT8,8B acetylate BACE1 ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5693001

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



N-acetyltransferase 8 and 8B (NAT8, 8B) can mediate the molecular stabilisation of BACE1, the membrane protein that acts as the rate-limiting enzyme in the generation of the Alzheimer disease amyloid beta-peptide. Specifically, nascent BACE1 is transiently acetylated on seven lysine residues in the ER lumen which protects the nascent protein from degradation in the ER Golgi intermediate compartment (ERGIC) and allows it to reach the Golgi apparatus (Ko & Puglielli 2009, Costantini et al. 2007). Lysine-acetylated BACE1 (7K-BACE1) is deacetylated in the Golgi apparatus.

Literature references

Costantini, C., Ko, MH., Jonas, MC., Puglielli, L. (2007). A reversible form of lysine acetylation in the ER and Golgi lumen controls the molecular stabilization of BACE1. *Biochem. J., 407*, 383-95. ↗

Ko, MH., Puglielli, L. (2009). Two endoplasmic reticulum (ER)/ER Golgi intermediate compartment-based lysine acetyltransferases post-translationally regulate BACE1 levels. *J. Biol. Chem., 284*, 2482-92. ↗

Editions

2015-05-13	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

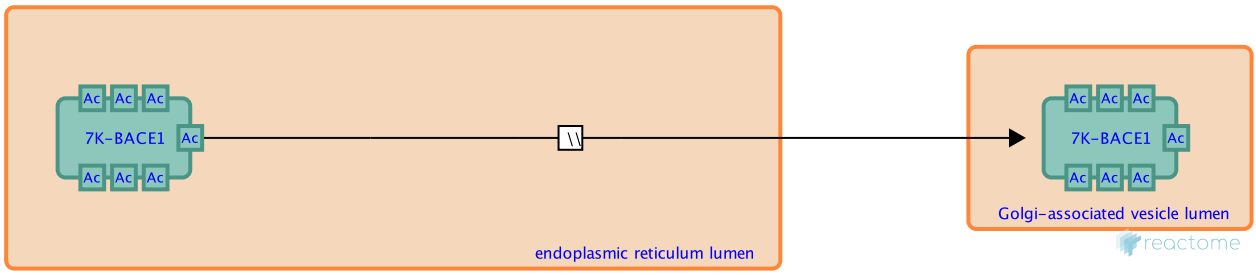
BACE1 translocates from ER lumen to Golgi apparatus ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5693071

Type: omitted

Compartments: endoplasmic reticulum lumen, plasma membrane



Beta secretase 1 (BACE1) is acetylated on 7 lysine residues inthe ER lumen (7K-BACE1). This protects the nascent protein from degradation in the ER Golgi intermediate compartment (ERGIC) and allows it to reach the Golgi apparatus (Kandalepas & Vassar 2014). The mechanism of this translocation is unknown.

Followed by: FURIN cleaves 7K-BACE1 to 7K-BACE1(46-501)

Literature references

Kandalepas, PC., Vassar, R. (2014). The normal and pathologic roles of the Alzheimer's β-secretase, BACE1. *Curr Alzheimer Res, 11*, 441-9. ↗

Editions

2015-05-13	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

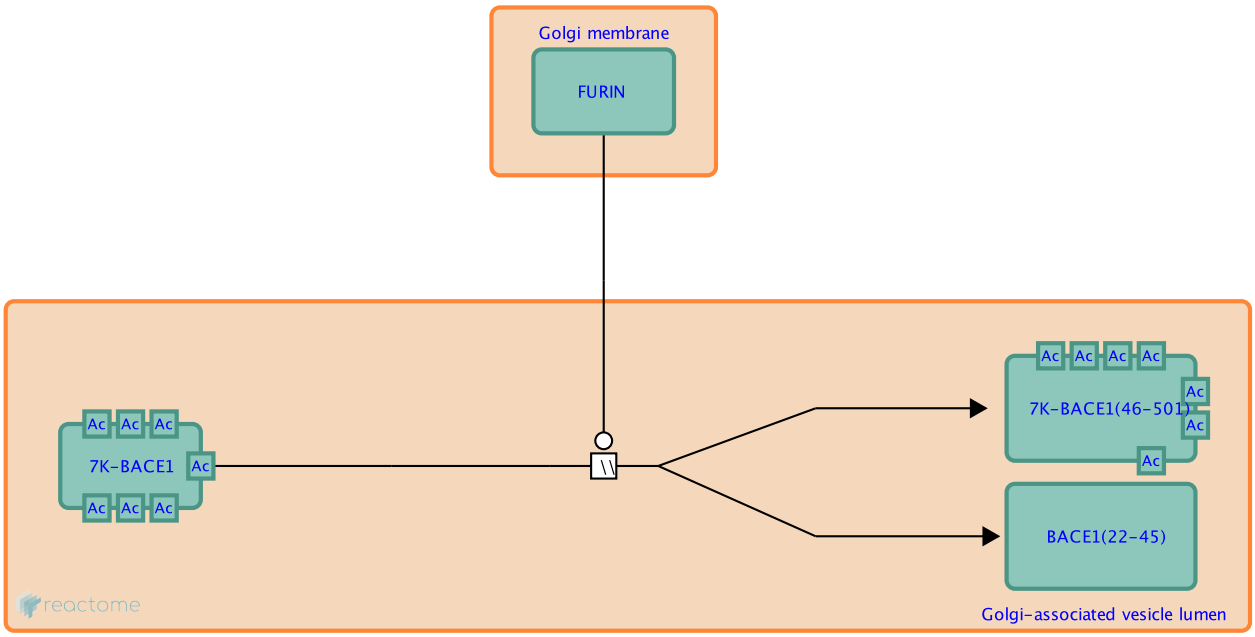
FURIN cleaves 7K-BACE1 to 7K-BACE1(46-501)

Location: Amyloid fiber formation

Stable identifier: R-HSA-5693081

Type: omitted

Compartments: Golgi-associated vesicle lumen, Golgi membrane



FURIN is the most likely endopeptidase that cleaves the BACE propeptide domain (BACE1(22-45)) to form the mature enzyme (7K-BACE1(46-501). Although the pro-enzyme possesses proteolytic activity, this activity is approximately doubled following removal of the prodomain (Bennett et al. 2000).

Preceded by: BACE1 translocates from ER lumen to Golgi apparatus

Followed by: Unknown deacetylase deacetylates 7K-BACE1(46-501)

Literature references

Bennett, BD., Denis, P., Haniu, M., Teplow, DB., Kahn, S., Louis, JC. et al. (2000). A furin-like convertase mediates propeptide cleavage of BACE, the Alzheimer's beta -secretase. *J. Biol. Chem., 275*, 37712-7.

Editions

2015-05-13	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

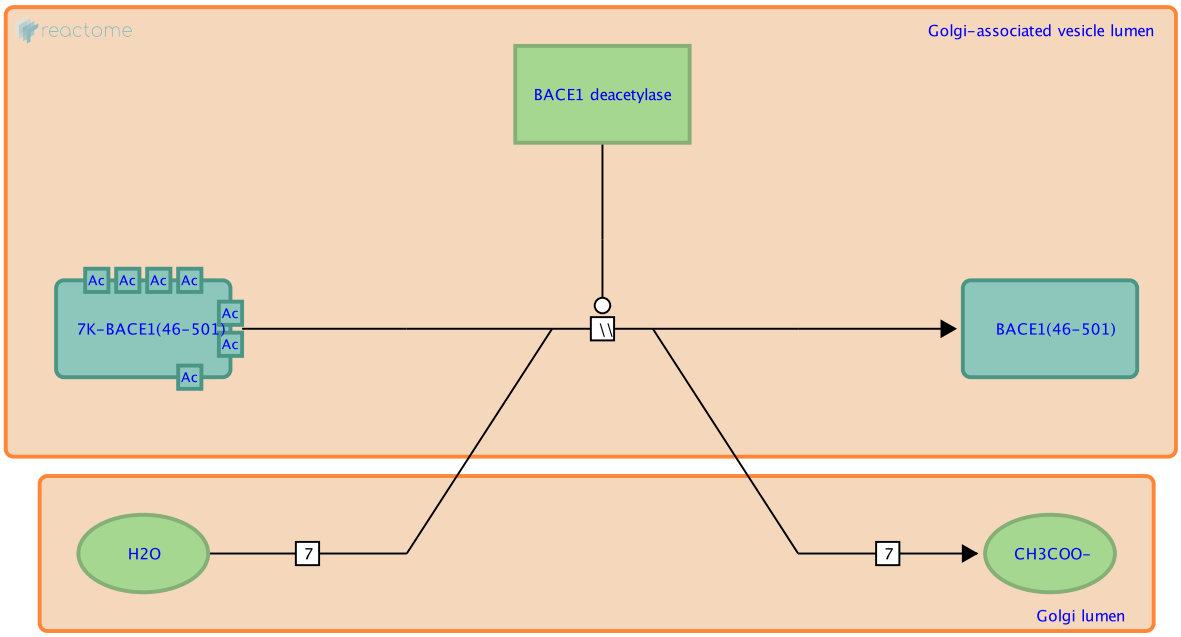
Unknown deacetylase deacetylates 7K-BACE1(46-501) ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5693092

Type: omitted

Compartments: Golgi-associated vesicle lumen



Mature beta secretase 1, acetylated on 7 lysine residues (7K-BACE1(46-501), is deacetylated by an unknown deacetylase in the Golgi apparatus (Kandalepas & Vassar 2014).

Preceded by: FURIN cleaves 7K-BACE1 to 7K-BACE1(46-501)

Followed by: BACE1(46-501) translocates from Golgi lumen to plasma membrane

Literature references

Kandalepas, PC., Vassar, R. (2014). The normal and pathologic roles of the Alzheimer's β-secretase, BACE1. *Curr Alzheimer Res, 11*, 441-9. ↗

Editions

2015-05-13	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

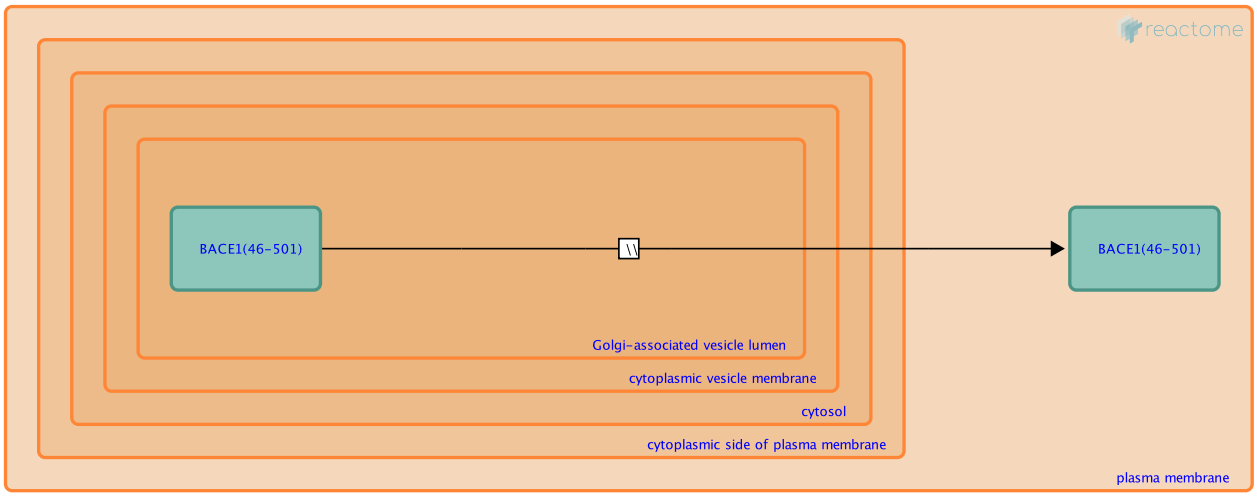
BACE1(46-501) translocates from Golgi lumen to plasma membrane ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5693086

Type: omitted

Compartments: Golgi-associated vesicle lumen, plasma membrane



BACE1(46-501) translocates from the Golgi lumen to the plasma membrane (Walter et al. 2001).

Preceded by: Unknown deacetylase deacetylates 7K-BACE1(46-501)

Followed by: BACE1 binds GGA1,2,3

Literature references

Walter, J., Hartung, B., Willem, M., Kaether, C., Capell, A., Lammich, S. et al. (2001). Phosphorylation regulates intracellular trafficking of beta-secretase. *J. Biol. Chem., 276*, 14634-41. ↗

Editions

2015-05-13	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

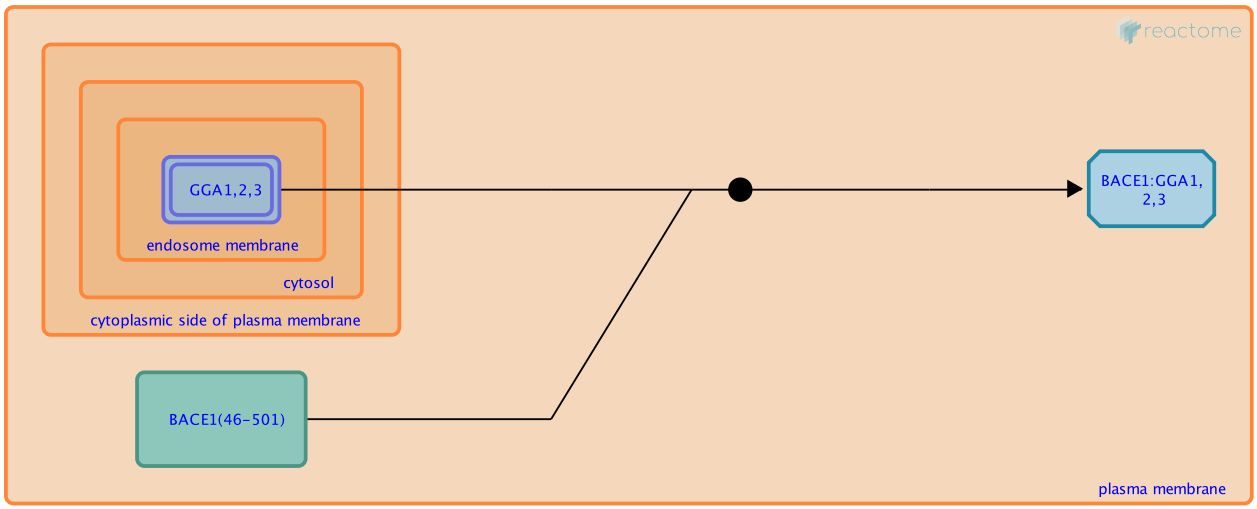
BACE1 binds GGA1,2,3 ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5692934

Type: binding

Compartments: plasma membrane, endosome membrane



Beta-secretase 1 (BACE1, memapsin-2) mediates the proteolytic processing of amyloid precursor protein (APP). BACE1 is transported from the plasma membrane to endosomes where APP hydrolysis takes place. The acid-cluster-dileucine (ACDL) motif in the cytosolic domain of BACE1 is able to bind to the VHS domain of ADP-ribosylation factor-binding proteins 1, 2 and 3 (GGA1,2,3) which play a role in protein sorting and trafficking between the trans-Golgi network (TGN) and endosomes. This is the presumed recognition step for BACE1 transport to endosomes (He et al. 2003).

Preceded by: BACE1(46-501) translocates from Golgi lumen to plasma membrane

Literature references

He, X., Zhu, G., Koelsch, G., Rodgers, KK., Zhang, XC., Tang, J. (2003). Biochemical and structural characterization of the interaction of memapsin 2 (beta-secretase) cytosolic domain with the VHS domain of GGA proteins. *Biochemistry, 42*, 12174-80. ↗

Editions

2015-05-13	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

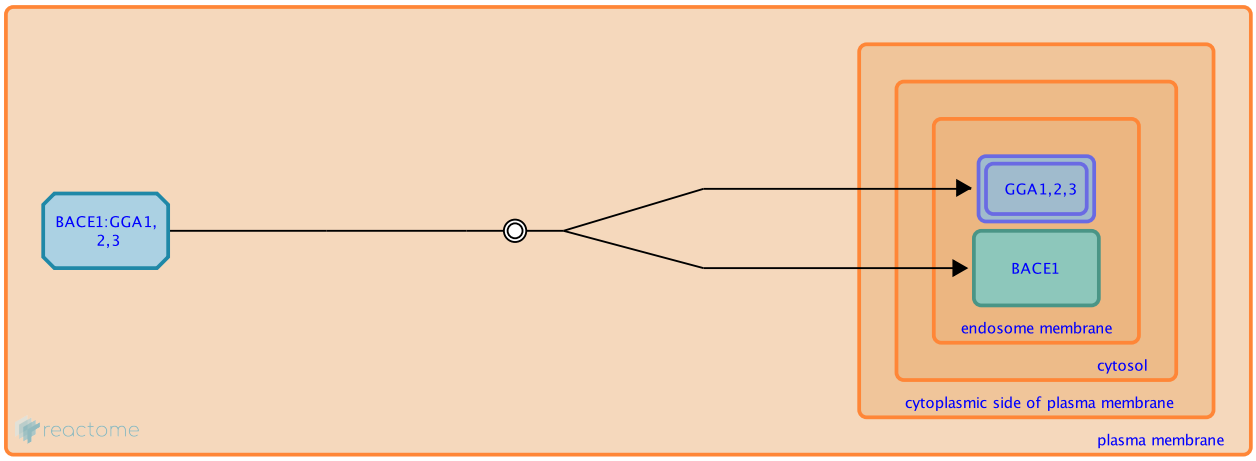
BACE1:GGA1,2,3 translocates from plasma membrane to endosome ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5692941

Type: dissociation

Compartments: plasma membrane, endosome membrane



Beta-secretase 1 (BACE1, memapsin-2) mediates the proteolytic processing of amyloid precursor protein (APP). BACE1 is transported from the cell surface to endosomes where APP hydrolysis takes place. The acid-cluster-dileucine (ACDL) motif in the cytosolic domain of BACE1 is able to bind to the VHS domain of ADP-ribosylation factor-binding proteins 1, 2 and 3 (GGA1,2,3) which play a role in protein sorting and trafficking between the trans-Golgi network (TGN) and endosomes. This is the presumed recognition step for BACE1 transport to endosomes (He et al. 2003).

Followed by: BACE1 cleaves APP(18-770) to APP(18-671) and APP(672-770)

Literature references

He, X., Zhu, G., Koelsch, G., Rodgers, KK., Zhang, XC., Tang, J. (2003). Biochemical and structural characterization of the interaction of memapsin 2 (beta-secretase) cytosolic domain with the VHS domain of GGA proteins. *Biochemistry, 42*, 12174-80. ↗

Editions

2015-05-13	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

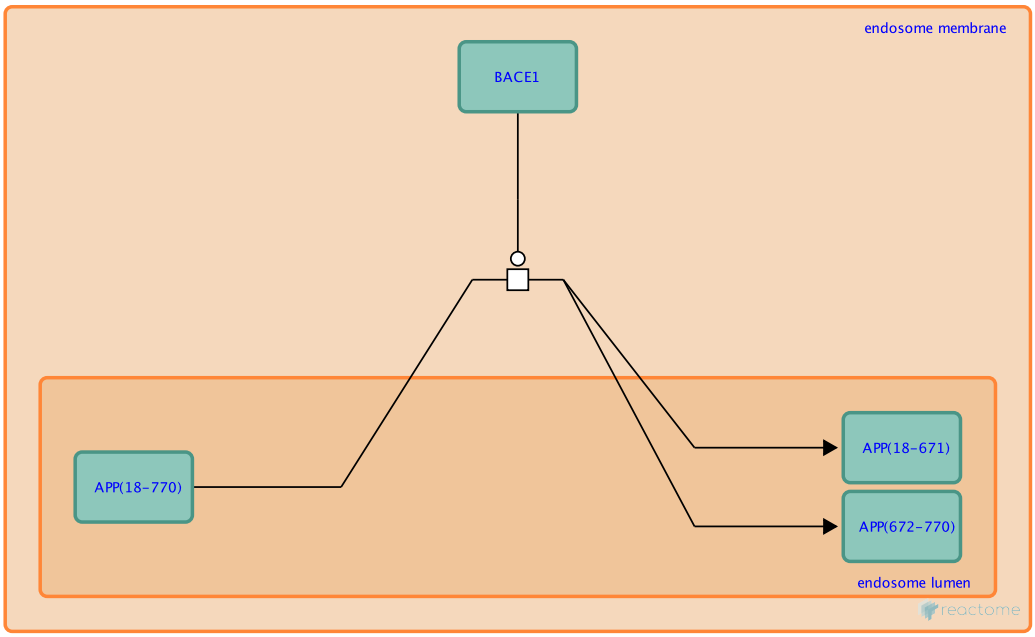
BACE1 cleaves APP(18-770) to APP(18-671) and APP(672-770) ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-5692495

Type: transition

Compartments: endosome membrane, endosome lumen



Amyloid precursor protein (APP(18-770)) is processed by one of two distinct proteolytic pathways; the non-amyloidogenic pathway where alpha-secretase cleaves APP at the cell surface within the A-beta domain, liberating APPs-alpha and the amyloidogenic pathway, where beta-secretase followed by gamma-secretase cleavages results in peptides which are the main fibril-forming peptides implicated in Alzheimer's disease. In the first step of the amyloidogenic pathway, the endosomal membrane protein beta-secretase 1 (BACE1) catalyses the cleavage of APP(18-770) within the ectodomain and liberates a soluble proteolytic fragment, termed soluble APP-beta (APPs-beta, APP(18-671)) and C99 (APP(672-770) (Baranello et al. 2015, Andrew et al. 2016). APP processing can occur in several endocytic and secretory pathways. For simplicity, the endosome has been chosen in this event.

Preceded by: BACE1:GGA1,2,3 translocates from plasma membrane to endosome, APP translocates from plasma membrane to endosome lumen

Followed by: Gamma-secretase cleaves APP(672-770) to APP(672-711) and APP(672-713)

Literature references

Baranello, RJ., Bharani, KL., Padmaraju, V., Chopra, N., Lahiri, DK., Greig, NH. et al. (2015). Amyloid-beta protein clearance and degradation (ABCD) pathways and their role in Alzheimer's disease. *Curr Alzheimer Res, 12,* 32-46. ↗

Editions

2015-05-12	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

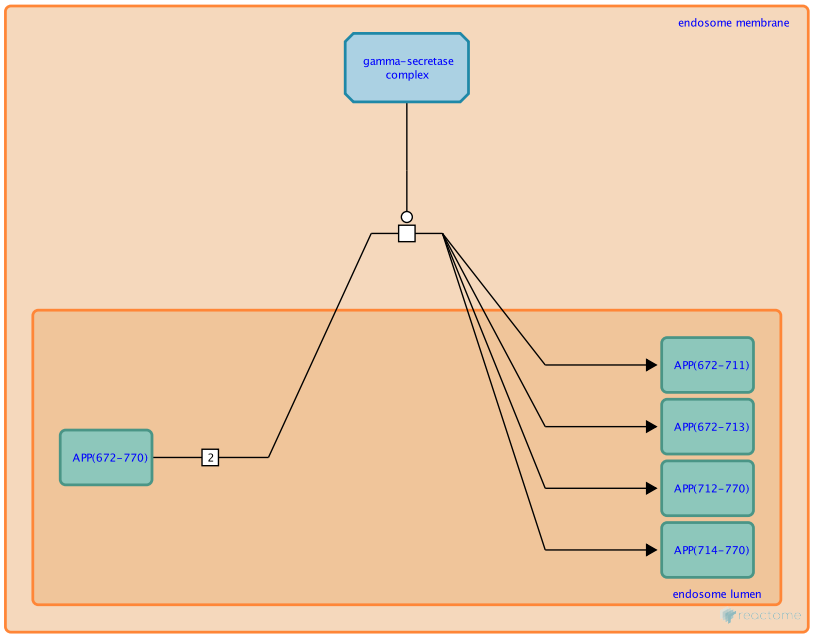
Gamma-secretase cleaves APP(672-770) to APP(672-711) and APP(672-713)

Location: Amyloid fiber formation

Stable identifier: R-HSA-9010096

Type: transition

Compartments: endosome membrane, endosome lumen



Beta secretase 1 (BACE1) catalyses the cleavage of APP(18 770) within the ectodomain and liberates a soluble proteolytic fragment, termed soluble APP beta (APPs beta, APP(18 671)) (Parvathy et al. 1999, Kinoshita et al. 2003). APPs beta is subsequently cleaved by the presenilin (PS) containing gamma secretase complex to eventually (step wise details of multiple cleavages not shown here) liberate the neurotoxic Abeta peptides 42 and 40 (APP(672 713) and APP(672 711) respectively) (Huse et al. 2002, Ehehalt et al. 2003, Anderson et al. 2005, Fukumori et al. 2006, Takami et al. 2009, Andrew et al. 2016).

Preceded by: BACE1 cleaves APP(18-770) to APP(18-671) and APP(672-770)

Followed by: APP(672-713),APP(672-711) translocate from endosome lumen to extracellular region

Literature references

Takami, M., Nagashima, Y., Sano, Y., Ishihara, S., Morishima-Kawashima, M., Funamoto, S. et al. (2009). gamma-Secretase: successive tripeptide and tetrapeptide release from the transmembrane domain of beta-carboxyl terminal fragment. *J. Neurosci., 29*, 13042-52.

Editions

2017-06-26	Authored, Edited	Jassal, B.
2018-08-10	Reviewed	Meras-Rios, A.

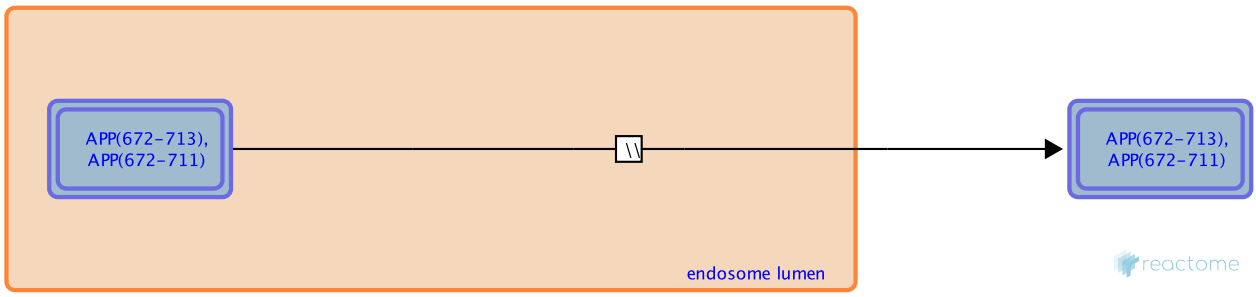
APP(672-713),APP(672-711) translocate from endosome lumen to extracellular region ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-6783332

Type: omitted

Compartments: endosome lumen, extracellular region



The Abeta peptides 42 and 40 (APP(672-713) and APP(673-711) respectively) are thought to be the main fibril-forming peptides implicated in neurodegenerative disorders. They translocate from the endosomal lumen to the extracellular region by an unknown mechanism (Qui et al. 2015, Baranello et al. 2015).

Preceded by: Gamma-secretase cleaves APP(672-770) to APP(672-711) and APP(672-713)

Followed by: Amyloid precursor proteins form ordered fibrils

Literature references

Qiu, T., Liu, Q., Chen, YX., Zhao, YF., Li, YM. (2015). Aβ42 and Aβ40: similarities and differences. *J. Pept. Sci.*. ↗

Baranello, RJ., Bharani, KL., Padmaraju, V., Chopra, N., Lahiri, DK., Greig, NH. et al. (2015). Amyloid-beta protein clearance and degradation (ABCD) pathways and their role in Alzheimer's disease. *Curr Alzheimer Res, 12,* 32-46. ↗

Editions

2015-06-12	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2015-11-09	Reviewed	Perry, G.

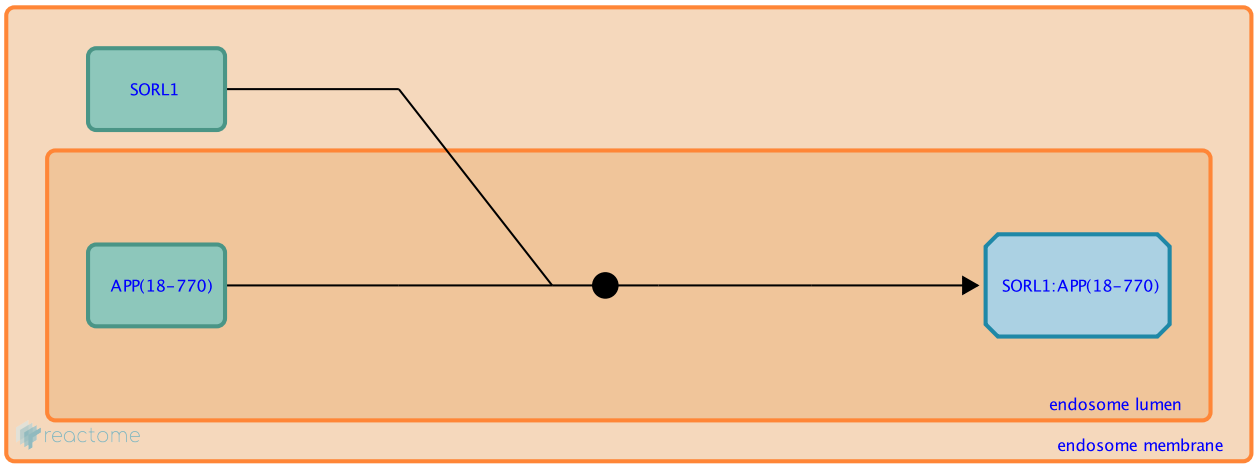
SORL1 binds APP(18-770)

Location: Amyloid fiber formation

Stable identifier: R-HSA-8871494

Type: binding

Compartments: endosome lumen, endosome membrane



The sortilin-related receptor (SORL1) is expressed mainly in brain, where it is most abundant in the cerebellum, cerebral cortex and the occipital pole. It acts as a sorting receptor that mediates anterograde and retrograde movement of APP between the trans-Golgi network and early endosomes, thereby restricting delivery of the APP precursor to endocytic compartments that favour amyloidogenic peptide production (Andersen et al. 2005, Willnow & Andersen 2013, Yin et al. 2015, Hermey 2015). Targeting SORL1 might present novel opportunities for Alzheimer's disease therapy.

Literature references

Andersen, OM., Reiche, J., Schmidt, V., Gotthardt, M., Spoelgen, R., Behlke, J. et al. (2005). Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein. *Proc. Natl. Acad. Sci. U.S.A., 102*, 13461-6.

Willnow, TE., Andersen, OM. (2013). Sorting receptor SORLA--a trafficking path to avoid Alzheimer disease. *J. Cell. Sci., 126*, 2751-60.

Yin, RH., Yu, JT., Tan, L. (2015). The Role of SORL1 in Alzheimer's Disease. *Mol. Neurobiol., 51*, 909-18.

Hermey, G. (2015). Intracellular sorting pathways of the amyloid precursor protein provide novel neuroprotective strategies. *Neural Regen Res, 10*, 1727-8.

Editions

2016-05-17	Authored, Edited	Jassal, B.
2016-07-15	Reviewed	D'Eustachio, P.

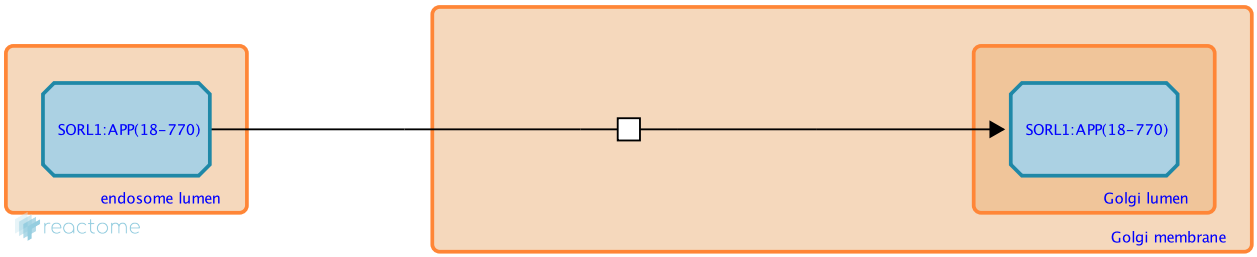
SORL1 transports APP(18-770) from endosome lumen to Golgi lumen

Location: Amyloid fiber formation

Stable identifier: R-HSA-8871506

Type: transition

Compartments: Golgi membrane, endosome membrane



The sortilin-related receptor (SORL1) is expressed mainly in brain, where it is most abundant in the cerebellum, cerebral cortex and the occipital pole. It acts as a sorting receptor that mediates anterograde and retrograde movement of APP between the trans-Golgi network and early endosomes, thereby restricting delivery of the APP precursor to endocytic compartments that favour amyloidogenic peptide production (Andersen et al. 2005, Willnow & Andersen 2013, Yin et al. 2015, Hermey 2015). Targeting SORL1 might present novel opportunities for Alzheimer's disease therapy.

Literature references

Andersen, OM., Reiche, J., Schmidt, V., Gotthardt, M., Spoelgen, R., Behlke, J. et al. (2005). Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein. *Proc. Natl. Acad. Sci. U.S.A., 102*, 13461-6.

Willnow, TE., Andersen, OM. (2013). Sorting receptor SORLA--a trafficking path to avoid Alzheimer disease. *J. Cell. Sci., 126*, 2751-60.

Yin, RH., Yu, JT., Tan, L. (2015). The Role of SORL1 in Alzheimer's Disease. *Mol. Neurobiol., 51*, 909-18.

Hermey, G. (2015). Intracellular sorting pathways of the amyloid precursor protein provide novel neuroprotective strategies. *Neural Regen Res, 10*, 1727-8.

Editions

2016-05-17	Authored, Edited	Jassal, B.
2016-07-15	Reviewed	D'Eustachio, P.

Amyloid precursor proteins form ordered fibrils ↗

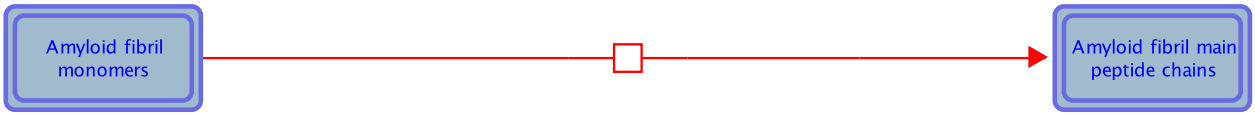
Location: Amyloid fiber formation

Stable identifier: R-HSA-977136

Type: transition

Compartments: extracellular region

Diseases: Amyloidosis



Amyloid fibril formation is associated with a wide range of diseases (Chiti & Dobson 2006), though the accumulation and deposition of fibrillar material does not correlate well with disease pathogenesis and it is now widely believed that oligomeric amyloid forms are largely responsible for the cytotoxic effects of amyloid (Glabe 2009). Fibrils have been described as more like crystalline polymer structures than the protein monomers they are derived from (Wetzel et al. 2007). In vitro, fibril formation is usually preceded by the association of monomers into oligomeric structures (Kodali & Wetzel 2007), though this remains to be established in vivo. Amyloid-beta forms spherical structures with around 12 units (Bernstein et al. 2005). Larger structures called protofibrils are also observed, non-spherical filamentous structures lacking a periodic substructure (Goldsbury 2005).

Preceded by: APP(672-713),APP(672-711) translocate from endosome lumen to extracellular region

Followed by: Amyloid fibrils have additional components

Literature references

Myatt, EA., Westholm, FA., Weiss, DT., Solomon, A., Schiffer, M., Stevens, FJ. (1994). Pathogenic potential of human monoclonal immunoglobulin light chains: relationship of in vitro aggregation to in vivo organ deposition. *Proc Natl Acad Sci U S A, 91*, 3034-8. ↗

El-Agnaf, OM., Jakes, R., Curran, MD., Wallace, A. (1998). Effects of the mutations Ala30 to Pro and Ala53 to Thr on the physical and morphological properties of alpha-synuclein protein implicated in Parkinson's disease. *FEBS Lett, 440*, 67-70. ↗

Eulitz, M., Weiss, DT., Solomon, A. (1990). Immunoglobulin heavy-chain-associated amyloidosis. *Proc Natl Acad Sci U S A, 87*, 6542-6. ↗

Gejyo, F., Homma, N., Suzuki, Y., Arakawa, M. (1986). Serum levels of beta 2-microglobulin as a new form of amyloid protein in patients undergoing long-term hemodialysis. *N Engl J Med, 314*, 585-6. ↗

Costa, PP., Figueira, AS., Bravo, FR. (1978). Amyloid fibril protein related to prealbumin in familial amyloidotic polyneuropathy. *Proc Natl Acad Sci U S A, 75*, 4499-503. ↗

Editions

2010-10-15	Authored	Jupe, S.
2011-04-08	Edited	Jupe, S.
2011-04-08	Reviewed	Perry, G.
2015-11-09	Reviewed	Perry, G.

Amyloid fibrils have additional components ↗

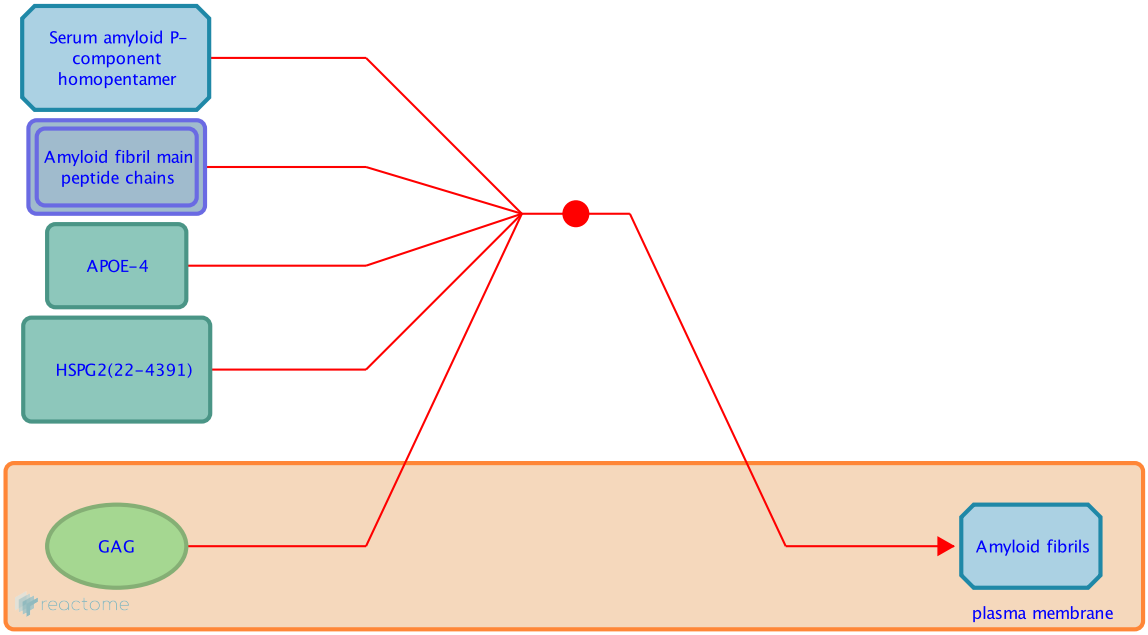
Location: Amyloid fiber formation

Stable identifier: R-HSA-976734

Type: binding

Compartments: extracellular region

Diseases: Amyloidosis



In addition to the main fibril peptide, mature amyloid fibrils have additional components. Serum amyloid P component (SAP) binds to all types of amyloid fibrils and is a universal constituent of amyloid deposits. SAP binding protects amyloid fibrils from proteolytic degradation (Tennent et al. 1995, Westermark 2005). SAP may function as a chaperone for amyloid formation (Coker et al. 2000).

Glycosaminoglycans (GAGs) and proteoglycans are found associated with all types of amyloid deposits (Alexandrescu 2005). Of the different types of GAG heparan sulfate and dermatan sulfate are the most prominent in amyloid deposits (Hirschfield & Hawkins, 2003). GAGs have been implicated in the nucleation of fibrils, they can also stabilize mature fibrils against dissociation (Yamaguchi et al. 2003) and proteolytic degradation (Gupta-Bansal et al. 1995).

Perlecan coimmunolocalizes with all types of amyloids (Snow & Wright 1989), accelerating fibril formation (Castillo et al. 1998), stabilizing them once formed (Castillo et al. 1997), and protecting them from proteolytic degradation (Gupta-Bansal et al. 1995).

APOE isoform 4 binds tightly to soluble ABeta peptide forming complexes that resist dissociation; it also binds to ABeta in its fibril form (Bales et al. 2002).

Preceded by: Serum amyloid P-component forms homopentamers, Amyloid precursor proteins form ordered fibrils

Literature references

Pepys, MB., Dyck, RF., de Beer, FC., Skinner, M., Cohen, AS. (1979). Binding of serum amyloid P-component (SAP) by amyloid fibrils. *Clin Exp Immunol, 38*, 284-93. ↗

Pepys, MB., Booth, DR., Hutchinson, WL., Gallimore, J., Collins, PM., Hohenester, E. (1997). Amyloid P component. A critical review. *Amyloid, 4*.

Zhang, X., Li, JP. (2010). Heparan sulfate proteoglycans in amyloidosis. *Prog Mol Biol Transl Sci, 93*, 309-34. ↗

Snow, AD., Kisilevsky, R. (1985). Temporal relationship between glycosaminoglycan accumulation and amyloid deposition during experimental amyloidosis. A histochemical study. *Lab Invest, 53*, 37-44. ↗

McLaurin, J., Franklin, T., Zhang, X., Deng, J., Fraser, PE. (1999). Interactions of Alzheimer amyloid-beta peptides with glycosaminoglycans effects on fibril nucleation and growth. *Eur J Biochem, 266*, 1101-10. ↗

Editions

2010-10-15	Authored	Jupe, S.
2011-04-08	Edited	Jupe, S.
2011-04-08	Reviewed	Perry, G.
2015-11-09	Reviewed	Perry, G.

Formation of serum amyloid P decamer ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-976817

Type: binding

Compartments: extracellular region

At physiological pH serum amyloid P component is a decamer of two pentameric rings lying face to face. This non-covalent interaction is readily dissociated by reducing the pH.

Preceded by: Serum amyloid P-component forms homopentamers

Literature references

Emsley, J., White, HE., O'Hara, BP., Oliva, G., Srinivasan, N., Tickle, IJ. et al. (1994). Structure of pentameric human serum amyloid P component. *Nature, 367*, 338-45. ↗

Editions

2010-10-15	Authored	Jupe, S.
2011-04-08	Edited	Jupe, S.
2011-04-08	Reviewed	Perry, G.
2015-11-09	Reviewed	Perry, G.

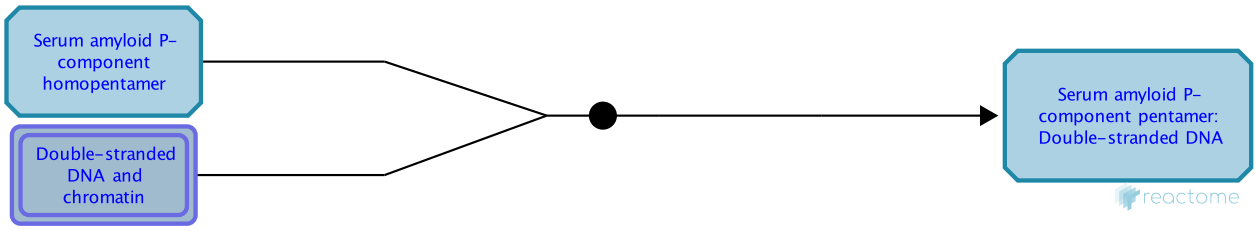
Serum amyloid P binds DNA and chromatin ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-977224

Type: binding

Compartments: extracellular region



Serum amyloid P component (SAP) binds DNA and chromatin in a calcium dependent manner in physiological conditions (Pepys et al. 1987). This binding displaces H1-type histones (Butler et al. 1990), solubilizing chromatin which is otherwise insoluble in extracellular fluids. SAP may therefore participate in the in vivo handling of chromatin exposed by cell death. SAP knockout mice spontaneously develop antinuclear autoimmunity and severe glomerulonephritis, a phenotype resembling human systemic lupus erythematosus, a serious autoimmune disease, suggesting that SAP binding may play a role in reducing the immunogenicity of chromatin and preventing autoimmunity (Bickerstaff et al. 1999).

Preceded by: Serum amyloid P-component forms homopentamers

Literature references

Pepys, MB., Butler, PJ. (1987). Serum amyloid P component is the major calcium-dependent specific DNA binding protein of the serum. *Biochem Biophys Res Commun, 148*, 308-13. ↗

Pepys, MB., Booth, SE., Tennent, GA., Butler, PJ., Williams, DG. (1994). Binding of pentraxins to different nuclear structures: C-reactive protein binds to small nuclear ribonucleoprotein particles, serum amyloid P component binds to chromatin and nucleoli. *Clin Exp Immunol, 97*, 152-7. ↗

Editions

2010-10-15	Authored	Jupe, S.
2011-04-08	Edited	Jupe, S.
2011-04-08	Reviewed	Perry, G.
2015-11-09	Reviewed	Perry, G.

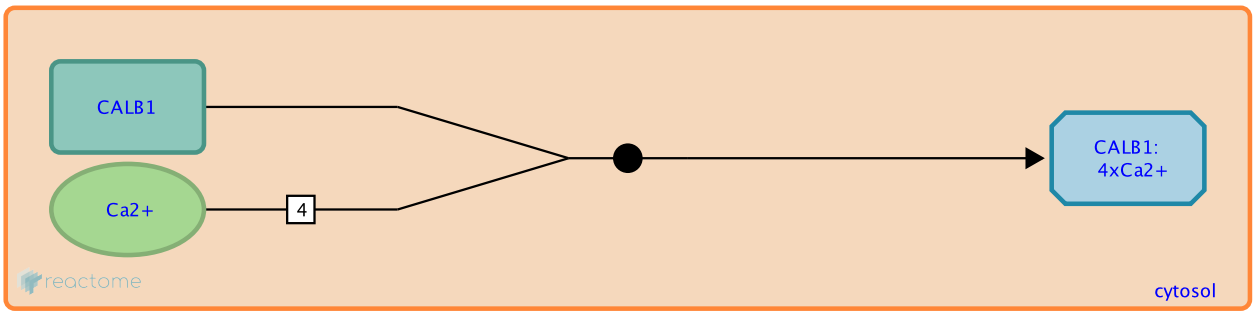
CALB1 binds 4xCa2+ ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-8932599

Type: binding

Compartments: cytosol



Calbindin (CALB1, aka D-28K, CAB27) is a calcium binding protein with six EF hand domains, functions as both a calcium buffer and a sensor protein and plays a vital role in neurological function. CALB1 binds four calcium ions at its four functional calcium-binding sites (EF hands 1,3,4 and 5), subsequently undergoing a conformational change. EF hands 2 and 6 are known not to bind calcium (Kojetin et al. 2006, Hobbs et al. 2009). Cholinergic neurons of the basal forebrain (BFCN) are selectively vulnerable in Alzheimer's disease (AD). Most of the BFCN in the human brain contain CALB1 and a large proportion lose their CALB1 in the course of normal aging. The BFCN which degenerate in AD lack CALB1, depriving neurons of the capacity to buffer high levels of intracellular calcium and thus leaving them vulnerable to pathological processes, such as those in AD, which can cause increased intracellular calcium, leading to their degeneration (Geula et al. 2003, Ahmadian et al. 2015).

Literature references

Kojetin, DJ., Venters, RA., Kordys, DR., Thompson, RJ., Kumar, R., Cavanagh, J. (2006). Structure, binding interface and hydrophobic transitions of Ca2+-loaded calbindin-D(28K). *Nat. Struct. Mol. Biol., 13*, 641-7. ↗

Hobbs, CA., Deterding, LJ., Perera, L., Bobay, BG., Thompson, RJ., Darden, TA. et al. (2009). Structural characterization of the conformational change in calbindin-D28k upon calcium binding using differential surface modification analyzed by mass spectrometry. *Biochemistry, 48*, 8603-14. ↗

Geula, C., Bu, J., Nagykery, N., Scinto, LF., Chan, J., Joseph, J. et al. (2003). Loss of calbindin-D28k from aging human cholinergic basal forebrain: relation to neuronal loss. *J. Comp. Neurol., 455*, 249-59. ↗

Ahmadian, SS., Rezvanian, A., Peterson, M., Weintraub, S., Bigio, EH., Mesulam, MM. et al. (2015). Loss of calbindin-D28K is associated with the full range of tangle pathology within basal forebrain cholinergic neurons in Alzheimer's disease. *Neurobiol. Aging, 36*, 3163-70. ↗

Editions

2016-07-27	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

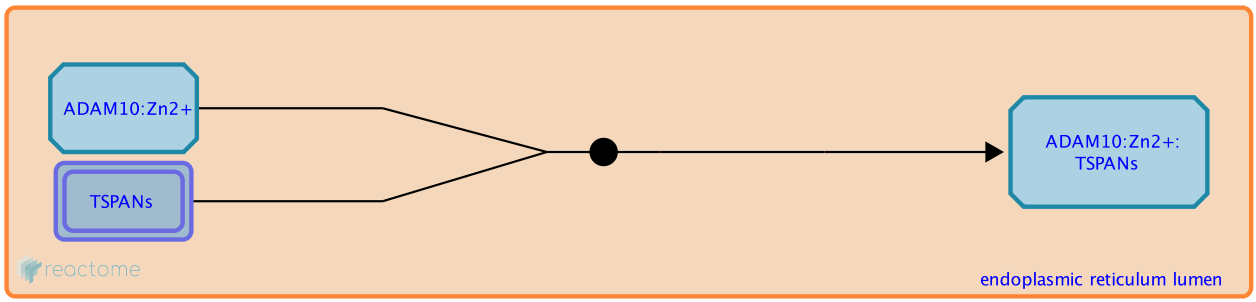
ADAM10:Zn2+ binds TSPANs ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-9010113

Type: binding

Compartments: endoplasmic reticulum lumen



The ADAM (A disintegrin and metalloprotease domain) family are membrane-anchored metalloproteases that mediate the proteolytic cleavage of many transmembrane proteins within their extracellular regions. This so-called ectodomain shedding plays an important role in many cell and developmental processes. ADAM10 (A Disintegrin and Metalloproteinase 10) has been identified as the major physiological alpha-secretase in neurons (Lammich et al. 1999, Kuhn et al. 2010), responsible for cleaving amyloid precursor protein (APP) in a non-amyloidogenic manner and producing APPs-alpha, a neuroprotective APP-derived peptide.

The trafficking of ADAM10 is regulated by a subgroup of the tetraspanin superfamily which have eight cysteines in the largest of the two extracellular domains and are referred to as TspanC8 tetraspanins. Tetraspanins associate specifically and directly with a limited number of proteins, and also with other tetraspanins, thereby generating a "tetraspanin web". Through these interactions, tetraspanins are believed to have a role in cell and membrane compartmentalisation (Charrin et al. 2014). TSPAN4, 14, 15 and 33 are thought to mediate ADAM10 exit from the ER and transport to the plasma membrane in a variety of ways (Noy et al. 2016, Jouannet et al. 2016).

Followed by: ADAM10:Zn2+:TSPANs translocates from ER lumen to plasma membrane

Literature references

Noy, PJ., Yang, J., Reyat, JS., Matthews, AL., Charlton, AE., Furmston, J. et al. (2016). TspanC8 Tetraspanins and A Disintegrin and Metalloprotease 10 (ADAM10) Interact via Their Extracellular Regions: EVIDENCE FOR DISTINCT BINDING MECHANISMS FOR DIFFERENT TspanC8 PROTEINS. *J. Biol. Chem., 291*, 3145-57. ↗

Jouannet, S., Saint-Pol, J., Fernandez, L., Nguyen, V., Charrin, S., Boucheix, C. et al. (2016). TspanC8 tetraspanins differentially regulate the cleavage of ADAM10 substrates, Notch activation and ADAM10 membrane compartmentalization. *Cell. Mol. Life Sci., 73*, 1895-915. ↗

Editions

2017-06-26	Authored, Edited	Jassal, B.
2018-08-10	Reviewed	Meras-Rios, A.

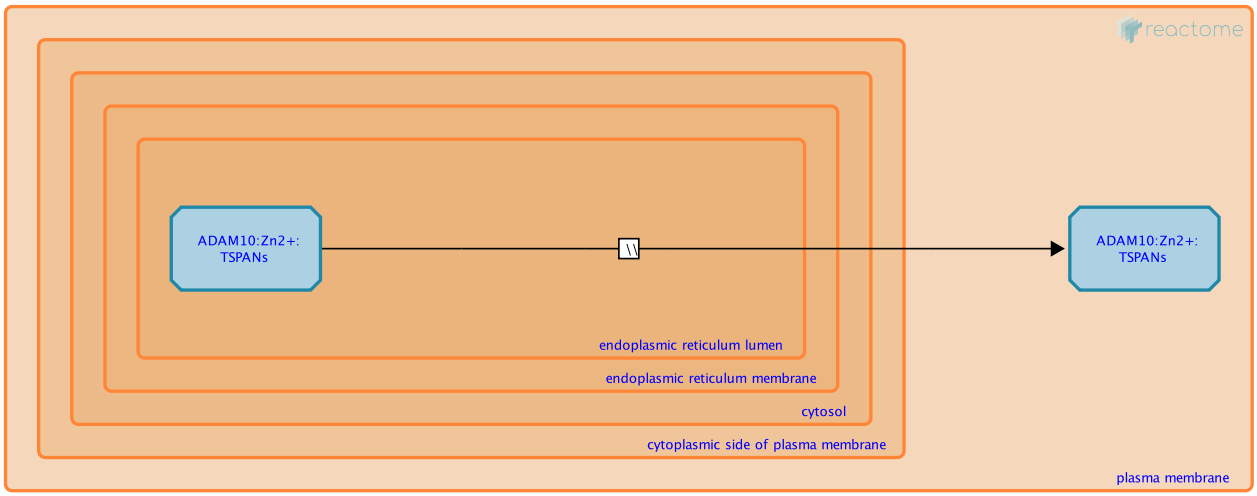
ADAM10:Zn2+:TSPANs translocates from ER lumen to plasma membrane ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-9010074

Type: omitted

Compartments: endoplasmic reticulum lumen, plasma membrane



The ADAM (A disintegrin and metalloprotease domain) family are membrane-anchored metalloproteases that mediate the proteolytic cleavage of many transmembrane proteins within their extracellular regions. This so-called ectodomain shedding plays an important role in many cell and developmental processes. ADAM10 (A Disintegrin and Metalloproteinase 10) has been identified as the major physiological alpha-secretase in neurons (Lammich et al. 1999, Kuhn et al. 2010), responsible for cleaving amyloid precursor protein (APP) in a non-amyloidogenic manner and producing APPs-alpha, a neuroprotective APP-derived peptide.

The trafficking of ADAM10 is regulated by a subgroup of the tetraspanin superfamily referred to as TspanC8 tetraspanins. TSPAN4, 14, 15 and 33 are thought to mediate ADAM10 exit from the ER and transport to the plasma membrane in a variety of ways (Noy et al. 2016, Jouannet et al. 2016).

Preceded by: ADAM10:Zn2+ binds TSPANs

Literature references

Noy, PJ., Yang, J., Reyat, JS., Matthews, AL., Charlton, AE., Furmston, J. et al. (2016). TspanC8 Tetraspanins and A Disintegrin and Metalloprotease 10 (ADAM10) Interact via Their Extracellular Regions: EVIDENCE FOR DISTINCT BINDING MECHANISMS FOR DIFFERENT TspanC8 PROTEINS. *J. Biol. Chem., 291*, 3145-57. ↗

Jouannet, S., Saint-Pol, J., Fernandez, L., Nguyen, V., Charrin, S., Boucheix, C. et al. (2016). TspanC8 tetraspanins differentially regulate the cleavage of ADAM10 substrates, Notch activation and ADAM10 membrane compartmentalization. *Cell. Mol. Life Sci., 73*, 1895-915. ↗

Editions

2017-06-26	Authored, Edited	Jassal, B.
2018-08-10	Reviewed	Meras-Rios, A.

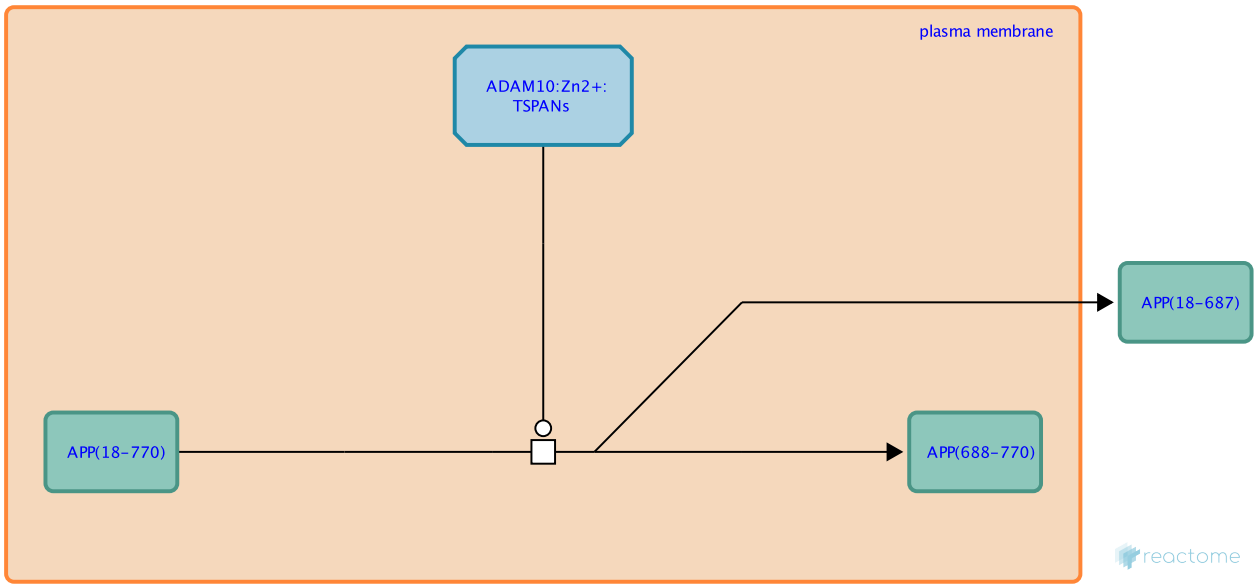
ADAM10:Zn2+:TSPANs cleaves APP(18-770)

Location: Amyloid fiber formation

Stable identifier: R-HSA-9010034

Type: transition

Compartments: plasma membrane, extracellular region



ADAM10 (A Disintegrin and Metalloproteinase 10) has been identified as the major physiological alpha-secretase in neurons (Lammich et al. 1999, Kuhn et al. 2010), responsible for cleaving amyloid precursor protein (APP(18-770)) in a non-amyloidogenic manner and producing APPs-alpha (APP(18-687), a neuro-protective APP-derived peptide (Mockett et al. 2017, Endres & Deller 2017). This cleavage also produces a cellular fragment, C83/CTF-alpha (APP(688-770). Cleavage by alpha-secretase at the cell surface is the major pathway in APP processing, accounting for 80–90% of APP turnover.

Literature references

Lammich, S., Kojro, E., Postina, R., Gilbert, S., Pfeiffer, R., Jasionowski, M. et al. (1999). Constitutive and regulated alpha-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease. *Proc. Natl. Acad. Sci. U.S.A., 96*, 3922-7.

Kuhn, PH., Wang, H., Dislich, B., Colombo, A., Zeitschel, U., Ellwart, JW. et al. (2010). ADAM10 is the physiologically relevant, constitutive alpha-secretase of the amyloid precursor protein in primary neurons. *EMBO J., 29*, 3020-32.

Editions

2017-06-26	Authored, Edited	Jassal, B.
2018-08-10	Reviewed	Meras-Rios, A.

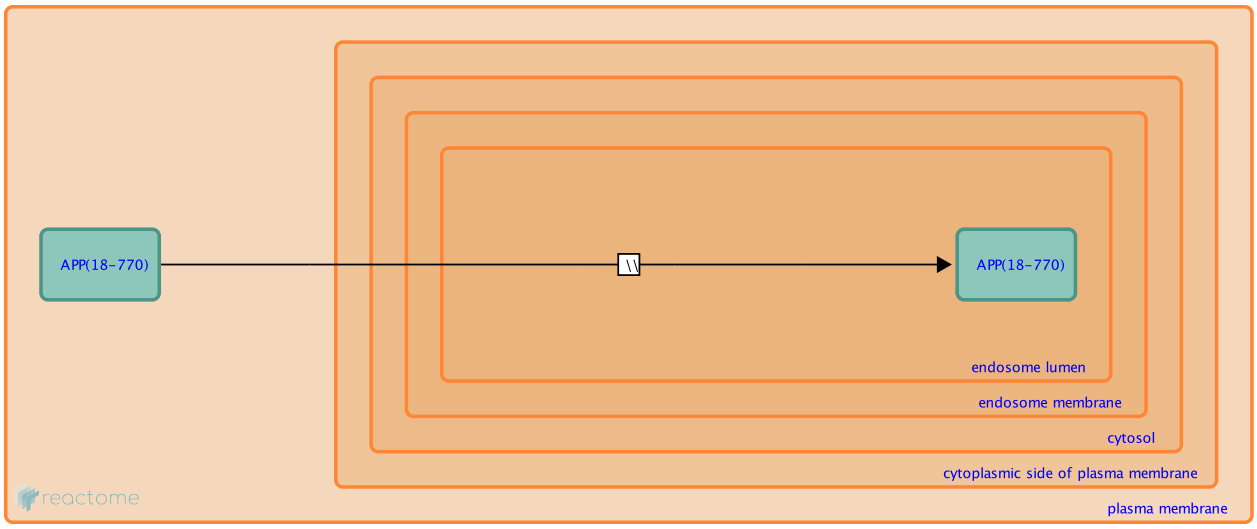
APP translocates from plasma membrane to endosome lumen ↗

Location: Amyloid fiber formation

Stable identifier: R-HSA-9010091

Type: omitted

Compartments: endosome lumen, plasma membrane



APP that does not get processed by alpha-secretase in the non-amyloidogenic pathway is internalised to endosomes for further processing (Baranello et al. 2015).

Followed by: BACE1 cleaves APP(18-770) to APP(18-671) and APP(672-770)

Literature references

Baranello, RJ., Bharani, KL., Padmaraju, V., Chopra, N., Lahiri, DK., Greig, NH. et al. (2015). Amyloid-beta protein clearance and degradation (ABCD) pathways and their role in Alzheimer's disease. *Curr Alzheimer Res, 12*, 32-46. ↗

Editions

2017-06-26	Authored, Edited	Jassal, B.
2018-08-10	Reviewed	Meras-Rios, A.

Table of Contents