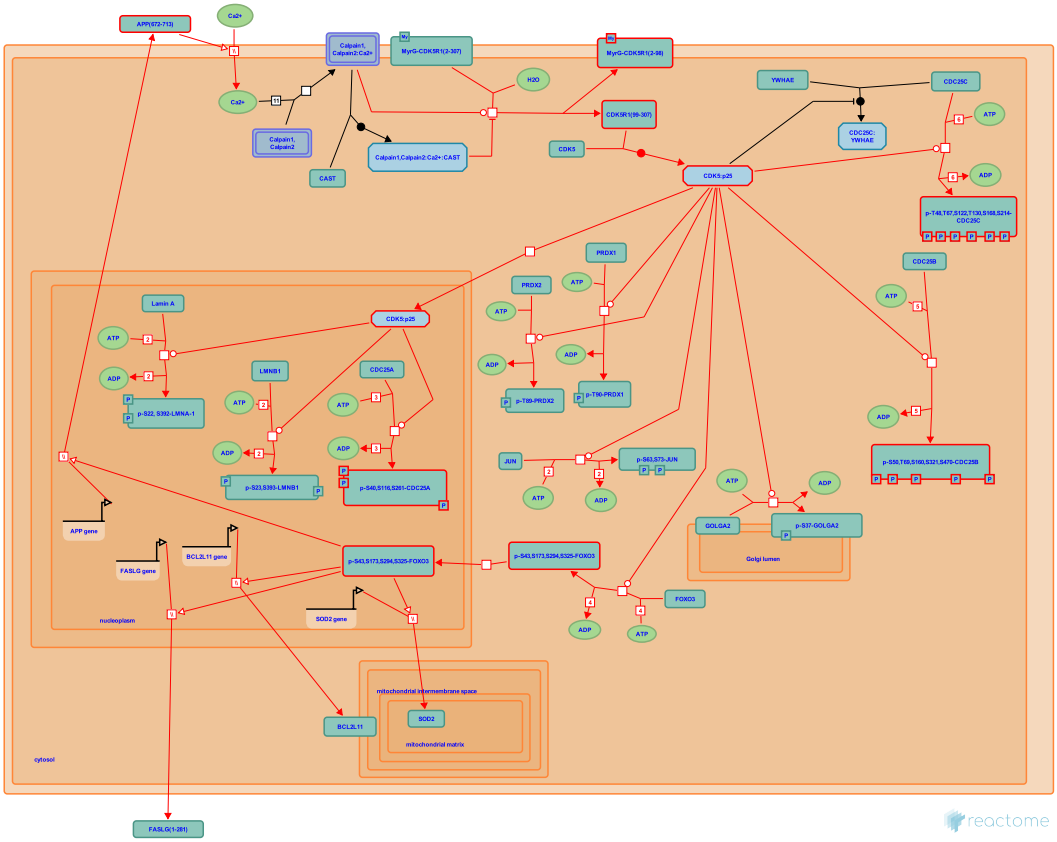
Deregulated CDK5 triggers multiple neuro-degenerative pathways in Alzheimer's disease models



Orlic-Milacic, M., Shah, K.

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

15/08/2020

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.

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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. ↗

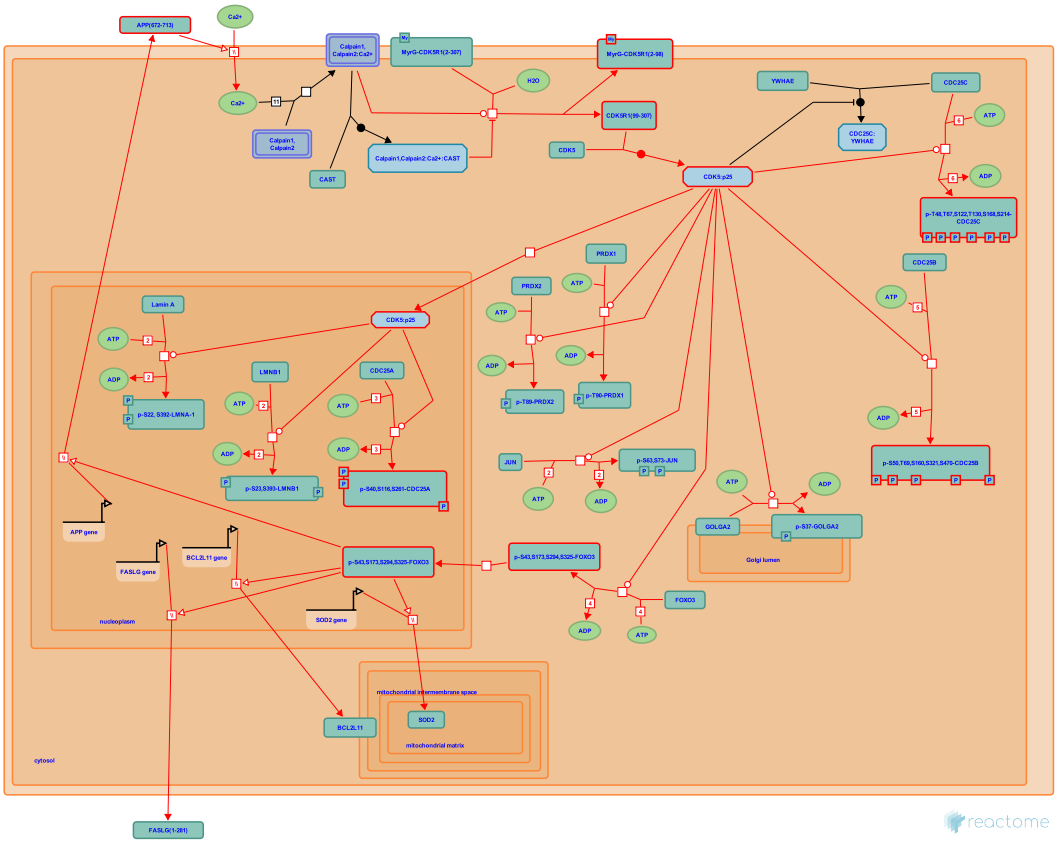
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models ↗

Stable identifier: R-HSA-8862803

Diseases: Alzheimer's disease



Post-mitotic neurons do not have an active cell cycle. However, deregulation of Cyclin Dependent Kinase-5 (CDK5) activity in these neurons can aberrantly activate various components of cell cycle leading to neuronal death (Chang et al. 2012). Random activation of cell cycle proteins has been shown to play a key role in the pathogenesis of several neurodegenerative disorders (Yang et al. 2003, Lopes et al. 2009). CDK5 is not activated by the canonical cyclins, but binds to its own specific partners, CDK5R1 and CDK5R2 (aka p35 and p39, respectively) (Tsai et al. 1994, Tang et al. 1995). Expression of p35 is nearly ubiquitous, whereas p39 is largely expressed in the central nervous system. A variety of neurotoxic insults such as beta-amyloid (A-beta), ischemia, excitotoxicity and oxidative stress disrupt the intracellular calcium homeostasis in neurons, thereby leading to the activation of calpain, which cleaves p35 into p25 and p10 (Lee et al. 2000). p25 has a six-fold longer half-life compared to p35 and lacks the membrane anchoring signal, which results in its constitutive activation and mislocalization of the CDK5:p25 complex to the cytoplasm and the nucleus. There, CDK5:p25 is able to access and phosphorylate a variety of atypical targets, triggering a cascade of neurotoxic pathways that culminate in neuronal death. One such neurotoxic pathway involves CDK5-mediated random activation of cell cycle proteins which culminate in neuronal death. Exposure of primary cortical neurons to oligomeric beta-amyloid (1-42) hyper-activates CDK5 due to p25 formation, which in turn phosphorylates CDC25A, CDC25B and CDC25C. CDK5 phosphorylates CDC25A at S40, S116 and S261; CDC25B at S50, T69, S160, S321 and S470; and CDC25C at T48, T67, S122, T130, S168 and S214. CDK5-mediated phosphorylation of CDC25A, CDC25B and CDC25C not only increases their phosphatase activities but also facilitates their release from 14-3-3 inhibitory binding. CDC25A, CDC25B and CDC25C in turn activate CDK1, CDK2 and CDK4 kinases causing neuronal death. Consistent with this mechanism, higher CDC25A, CDC25B and CDC25C activities were observed in human

Alzheimer's disease (AD) clinical samples, as compared to age-matched controls. Inhibition of CDC25 isoforms confers neuroprotection to beta-amyloid toxicity, which underscores the contribution of this pathway to AD pathogenesis

Literature references

Lee, MS., Kwon, YT., Li, M., Peng, J., Friedlander, RM., Tsai, LH. (2000). Neurotoxicity induces cleavage of p35 to p25 by calpain. *Nature, 405*, 360-4.

Lopes, JP., Oliveira, CR., Agostinho, P. (2009). Cell cycle re-entry in Alzheimer's disease: a major neuropathological characteristic?. *Curr Alzheimer Res, 6*, 205-12.

Yang, Y., Mufson, EJ., Herrup, K. (2003). Neuronal cell death is preceded by cell cycle events at all stages of Alzheimer's disease. *J. Neurosci., 23*, 2557-63.

Tang, D., Yeung, J., Lee, KY., Matsushita, M., Matsui, H., Tomizawa, K. et al. (1995). An isoform of the neuronal cyclin-dependent kinase 5 (Cdk5) activator. *J. Biol. Chem., 270*, 26897-903.

Tsai, LH., Delalle, I., Caviness, VS., Chae, T., Harlow, E. (1994). p35 is a neural-specific regulatory subunit of cyclin-dependent kinase 5. *Nature, 371*, 419-23.

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

Influx of extracellular calcium ↗

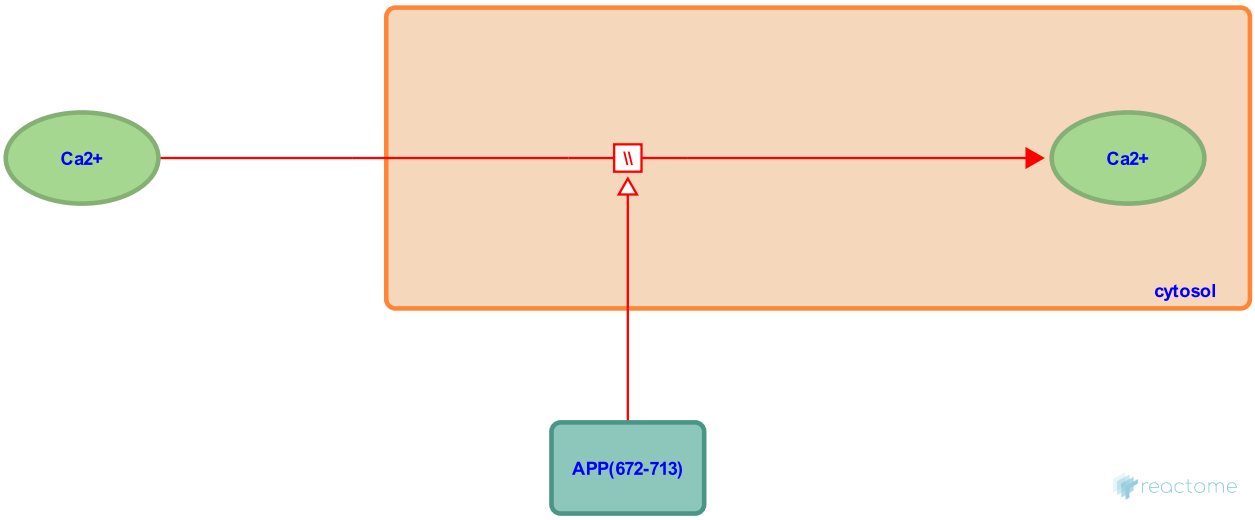
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863009

Type: omitted

Compartments: cytosol, extracellular region

Diseases: Alzheimer's disease



Beta amyloid increases influx of extracellular calcium (Ca2+) through the plasma membrane, thus increasing the cytosolic Ca2+ concentration. The mechanism has not been completely elucidated (Lee et al. 2000, Abramov et al. 2004).

Followed by: Calpain activation

Literature references

Abramov, AY., Canevari, L., Duchen, MR. (2004). Calcium signals induced by amyloid beta peptide and their consequences in neurons and astrocytes in culture. *Biochim. Biophys. Acta, 1742*, 81-7. ↗

Lee, MS., Kwon, YT., Li, M., Peng, J., Friedlander, RM., Tsai, LH. (2000). Neurotoxicity induces cleavage of p35 to p25 by calpain. *Nature, 405*, 360-4. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

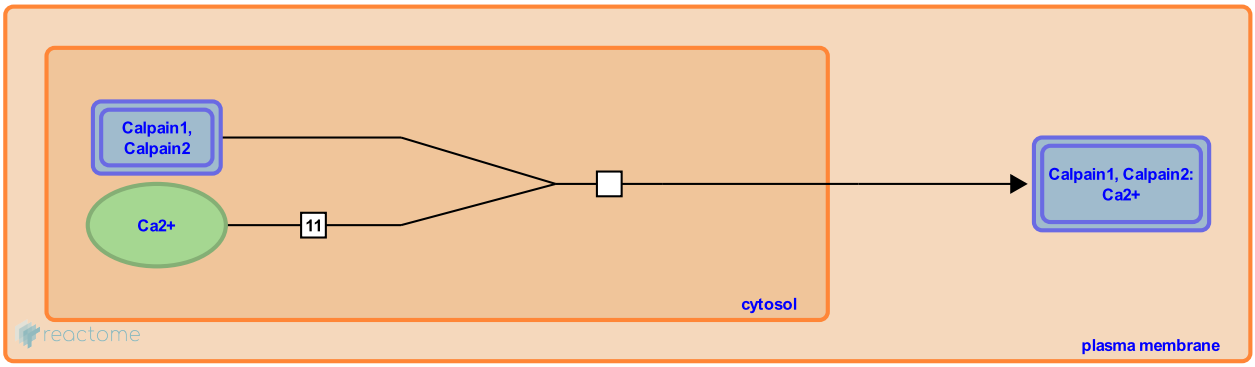
Calpain activation ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863008

Type: transition

Compartments: cytosol



Binding of calcium ions to the calpain dimer composed of the calpain catalytic subunit of 80 kDa and a calpain regulatory subunit of 30 kDa enables conformation change that results in formation of a functional catalytic center and also promotes relocalization of the calpain complex to the plasma membrane (Lin et al. 1997, Strobl et al. 2000, Schad et al. 2002). Calpain complexes involving the neuronally expressed mu-calpain (CAPN1) and m-calpain (CAPN2) catalytic subunits (Lee et al. 2000) are shown in this activation reaction.

Preceded by: Influx of extracellular calcium

Followed by: Calpain cleaves p35 to p25, CAST binds Ca2+ bound calpain

Literature references

Lee, MS., Kwon, YT., Li, M., Peng, J., Friedlander, RM., Tsai, LH. (2000). Neurotoxicity induces cleavage of p35 to p25 by calpain. *Nature, 405*, 360-4. ↗

Schád, E., Farkas, A., Jékely, G., Tompa, P., Friedrich, P. (2002). A novel human small subunit of calpains. *Biochem. J. , 362*, 383-8. ↗

Lin, GD., Chattopadhyay, D., Mäki, M., Wang, KK., Carson, M., Jin, L. et al. (1997). Crystal structure of calcium bound domain VI of calpain at 1.9 A resolution and its role in enzyme assembly, regulation, and inhibitor binding. *Nat. Struct. Biol., 4*, 539-47. ↗

Strobl, S., Fernandez-Catalan, C., Braun, M., Huber, R., Masumoto, H., Nakagawa, K. et al. (2000). The crystal structure of calcium-free human m-calpain suggests an electrostatic switch mechanism for activation by calcium. *Proc. Natl. Acad. Sci. U.S.A., 97*, 588-92. ↗

Editions

2016-02-23	Authored	Shah, K.
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Calpain cleaves p35 to p25 ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

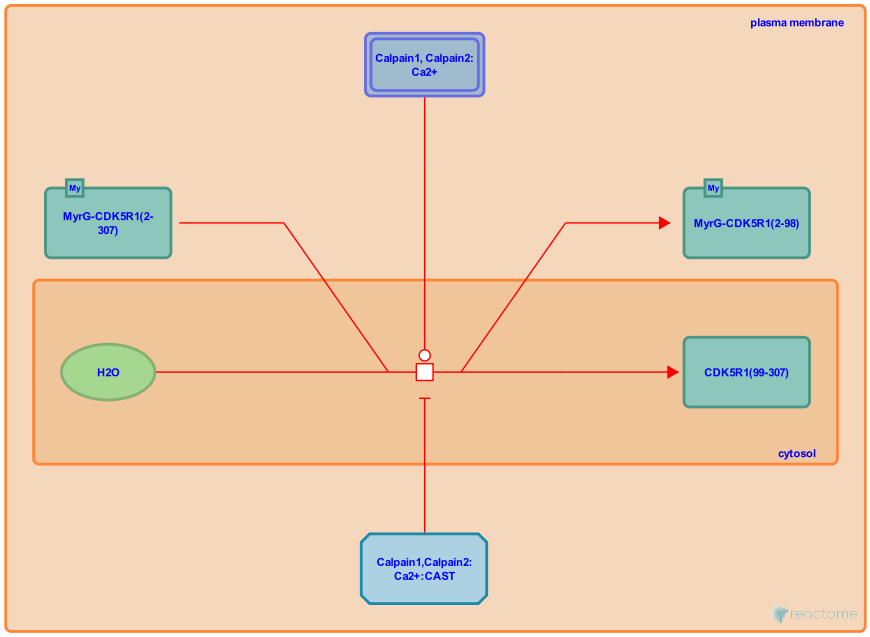
Stable identifier: R-HSA-8863012

Type: transition

Compartments: cytosol

Diseases: Alzheimer's disease

Inferred from: Calpain 1 or Calpain 2 cleaves Cdk5r1 (p35) (Mus musculus)



A variety of neurotoxic insults such as beta-amyloid (A-beta), ischemia, excitotoxicity and oxidative stress disrupt the intracellular calcium homeostasis in neurons, thereby leading to the activation of calpain, which cleaves p35 into p25 and p10 (Lee et al. 2000). p25 has a six-fold longer half-life compared to p35 and lacks the membrane anchoring signal, which results in its constitutive activation and mislocalization of the CDK5:p25 complex to the cytoplasm and the nucleus.

Calpain-mediated cleavage of p35 to p25 is inhibited by calpastatin (CAST). CAST levels are decreased in Alzheimer disease (Sato et al. 2011).

Preceded by: Calpain activation

Followed by: CDK5 binds p25

Literature references

Lee, MS., Kwon, YT., Li, M., Peng, J., Friedlander, RM., Tsai, LH. (2000). Neurotoxicity induces cleavage of p35 to p25 by calpain. *Nature, 405*, 360-4. ↗

Editions

2016-02-23	Authored	Shah, K.
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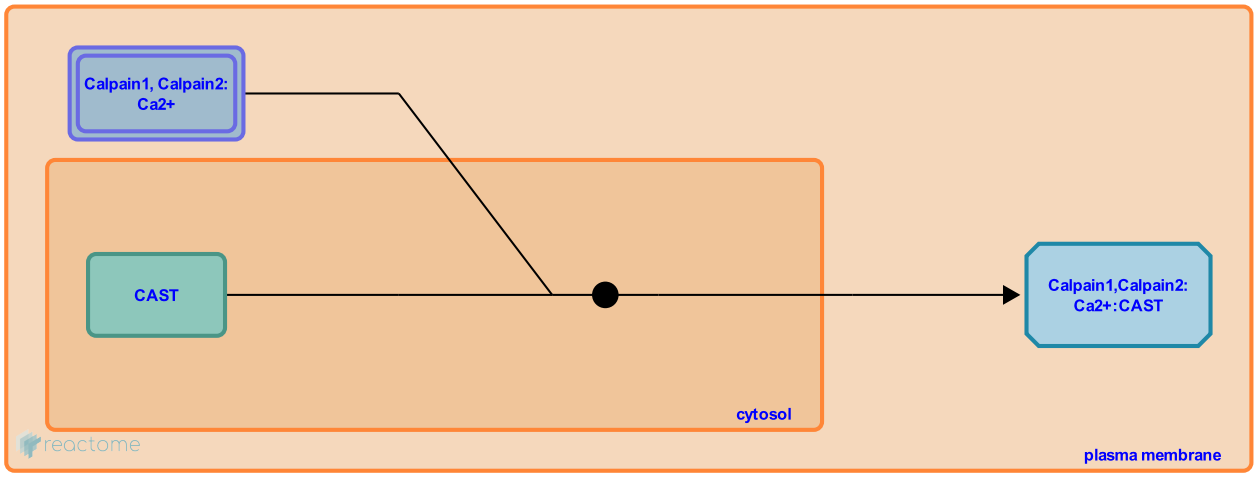
CAST binds Ca2+ bound calpain ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8868134

Type: binding

Compartments: cytosol, plasma membrane



The proteolytic activity of calpain complexes is inhibited by binding to calpastatin (CAST) (Takano et al. 1995). Based on detailed structural studies of recombinant rat proteins, CAST associates with calcium-bound calpain heterodimers and occupies both sides of the calpain active site cleft (Hanna et al. 2008). CAST levels are reduced in Alzheimer disease (Sato et al. 2011).

Preceded by: Calpain activation

Literature references

Takano, E., Ma, H., Yang, HQ., Mäki, M., Hatanaka, M. (1995). Preference of calcium-dependent interactions between calmodulin-like domains of calpain and calpastatin subdomains. *FEBS Lett., 362*, 93-7. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5 binds p25 ↗

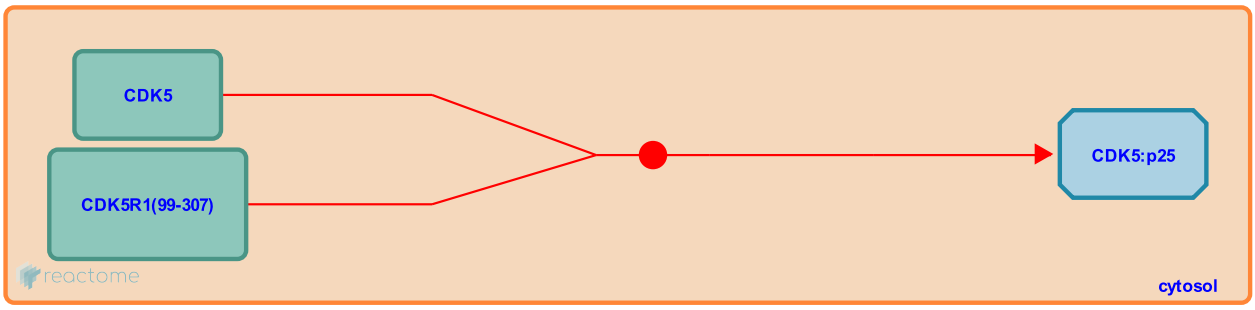
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863013

Type: binding

Compartments: cytosol

Diseases: Alzheimer's disease



p25 has a 5-10 fold longer half-life compared to p35 and lacks the membrane anchoring signal, which results in its constitutive activation and mislocalization of the CDK5:p25 complex to the cytoplasm and the nucleus (Patrick et al. 1999). As CDK5 deregulation triggers nuclear envelope dispersion (Chang et al. 2011), with timing being uncertain, all phosphorylation events catalyzed by the CDK5:p25 complex are shown to occur in the cytosol.

Preceded by: Calpain cleaves p35 to p25

Followed by: CDK5:p25 phosphorylates PRDX2, p25-bound CDK5 phosphorylates CDC25B, CDK5:p25 phosphorylates PRDX1, p25-bound CDK5 phosphorylates CDC25C, CDK5:p25 phosphorylates FOXO3, CDK5:p25 phosphorylates GOLGA2, CDK5:p25 translocates to the nucleus

Literature references

Patrick, GN., Zukerberg, L., Nikolic, M., de la Monte, S., Dikkes, P., Tsai, LH. (1999). Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. *Nature, 402*, 615-22. ↗

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p25-bound CDK5 phosphorylates CDC25A ↗

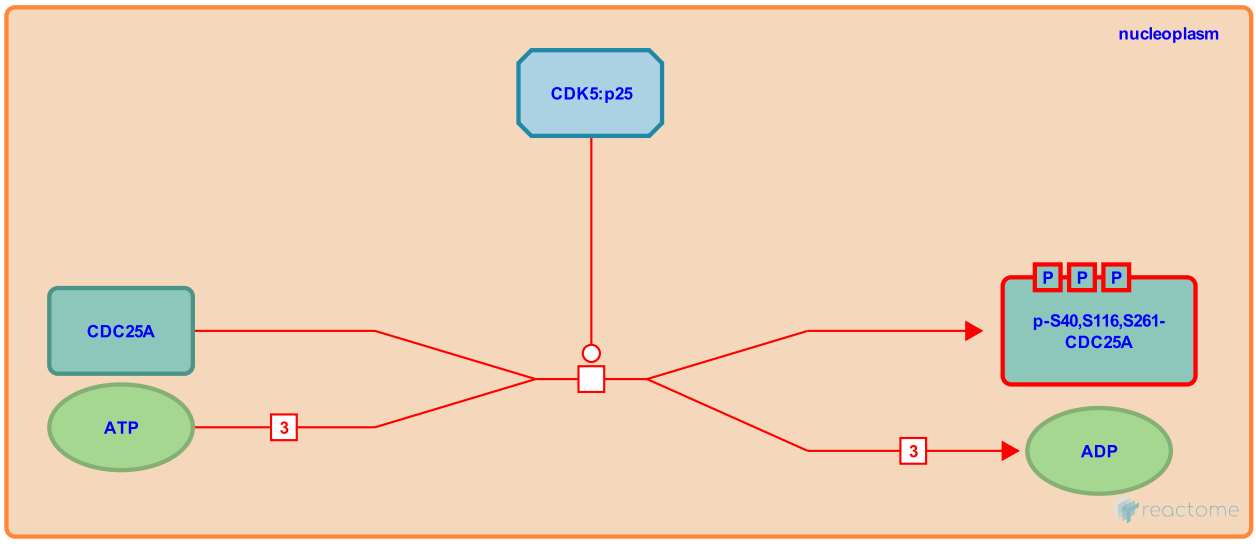
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863014

Type: transition

Compartments: nucleoplasm

Diseases: Alzheimer's disease



CDK5, activated by binding to p25, phosphorylates CDC25A protein tyrosine phosphatase at serine residues S40, S116 and S261. CDC25A mainly localizes to the nucleus in neurons and CDK5-mediated phosphorylation does not change its localization. Once activated by CDK5, CDC25A promotes activation of CDK1, CDK2 and CDK4 (Chang et al. 2012).

Preceded by: CDK5:p25 translocates to the nucleus

Literature references

Chang, KH., Vincent, F., Shah, K. (2012). Deregulated Cdk5 triggers aberrant activation of cell cycle kinases and phosphatases inducing neuronal death. *J. Cell. Sci., 125*, 5124-37. ↗

Editions

2016-02-23	Authored	Shah, K.
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p25-bound CDK5 phosphorylates CDC25B ↗

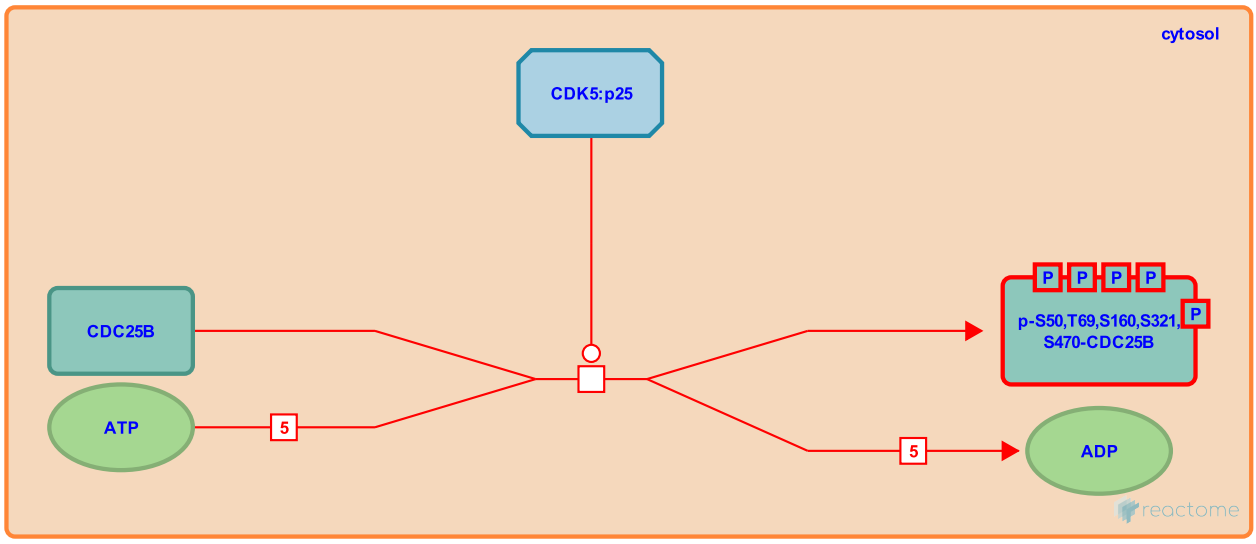
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863007

Type: transition

Compartments: cytosol

Diseases: Alzheimer's disease



CDK5, activated by binding to p25 phosphorylates CDC25B protein tyrosine phosphatase on serine and threonine residues S50, T69, S160, S321 and S470. In neurons, CDK25B localizes to both nucleus and cytosol and CDK5-mediated phosphorylation does not change its localization. Once activated by CDK5, CDC25B promotes activation of CDK1, CDK2 and CDK4 (Chang et al. 2012).

Preceded by: CDK5 binds p25

Literature references

Chang, KH., Vincent, F., Shah, K. (2012). Deregulated Cdk5 triggers aberrant activation of cell cycle kinases and phosphatases inducing neuronal death. *J. Cell. Sci., 125*, 5124-37. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

p25-bound CDK5 phosphorylates CDC25C ↗

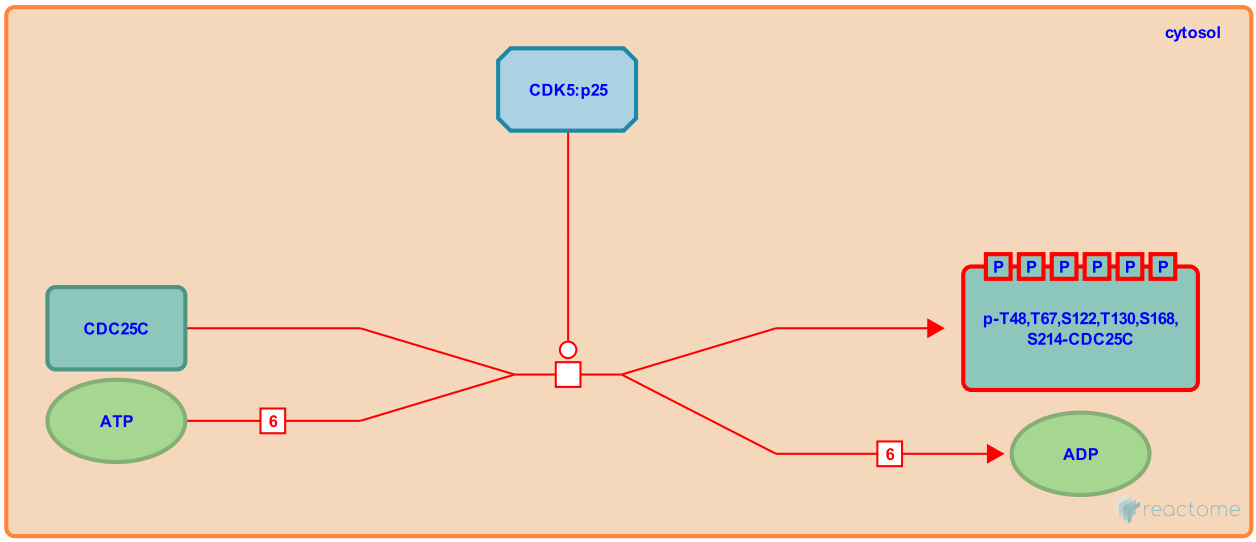
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863011

Type: transition

Compartments: cytosol

Diseases: Alzheimer's disease



CDK5 activated by binding to p25 phosphorylates CDC25C protein tyrosine phosphatase at serine and threonine residues T48, T67, S122, T130, S168, and S214. CDK5-mediated phosphorylation of CDC25C interferes with 14-3-3-epsilon (YWHAE) mediated retention of CDC25C in the cytosol. Once activated by CDK5, CDC25C promotes activation of CDK1 (Chang et al. 2012).

Preceded by: CDK5 binds p25

Literature references

Chang, KH., Vincent, F., Shah, K. (2012). Deregulated Cdk5 triggers aberrant activation of cell cycle kinases and phosphatases inducing neuronal death. *J. Cell. Sci., 125*, 5124-37. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

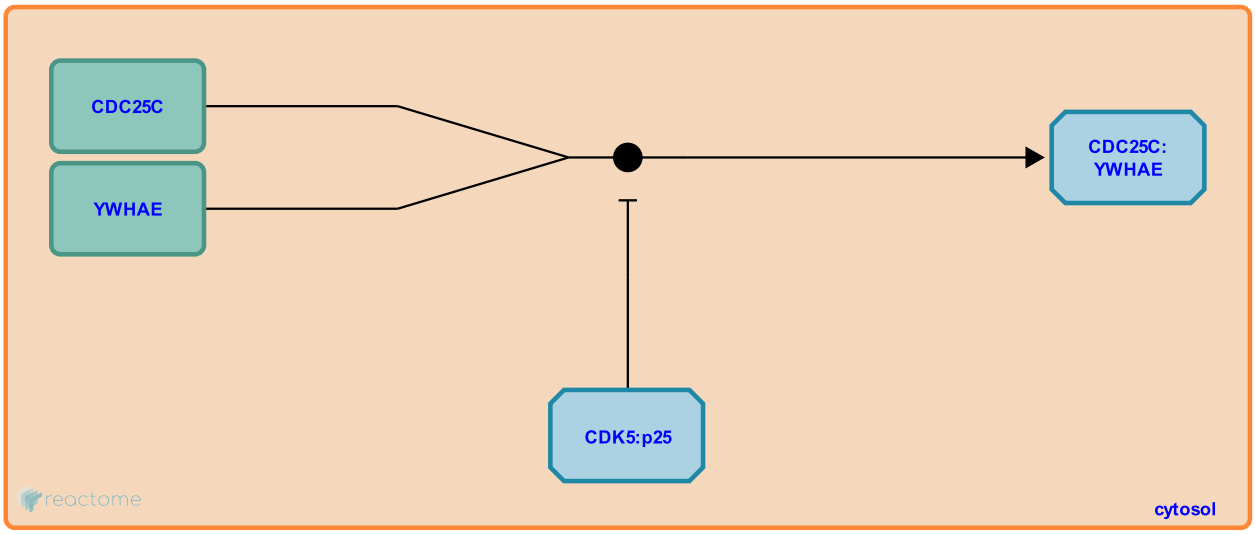
CDC25C binds YWHAE (14-3-3-epsilon) ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863674

Type: binding

Compartments: cytosol



Binding of CDC25C to 14-3-3-epsilon (YWHAE), which promotes retention of CDC25C in the cytosol, is inhibited by CDK5-mediated phosphorylation of CDC25C (Chang et al. 2012).

Literature references

Chang, KH., Vincent, F., Shah, K. (2012). Deregulated Cdk5 triggers aberrant activation of cell cycle kinases and phosphatases inducing neuronal death. *J. Cell. Sci., 125*, 5124-37. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5:p25 phosphorylates GOLGA2 ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

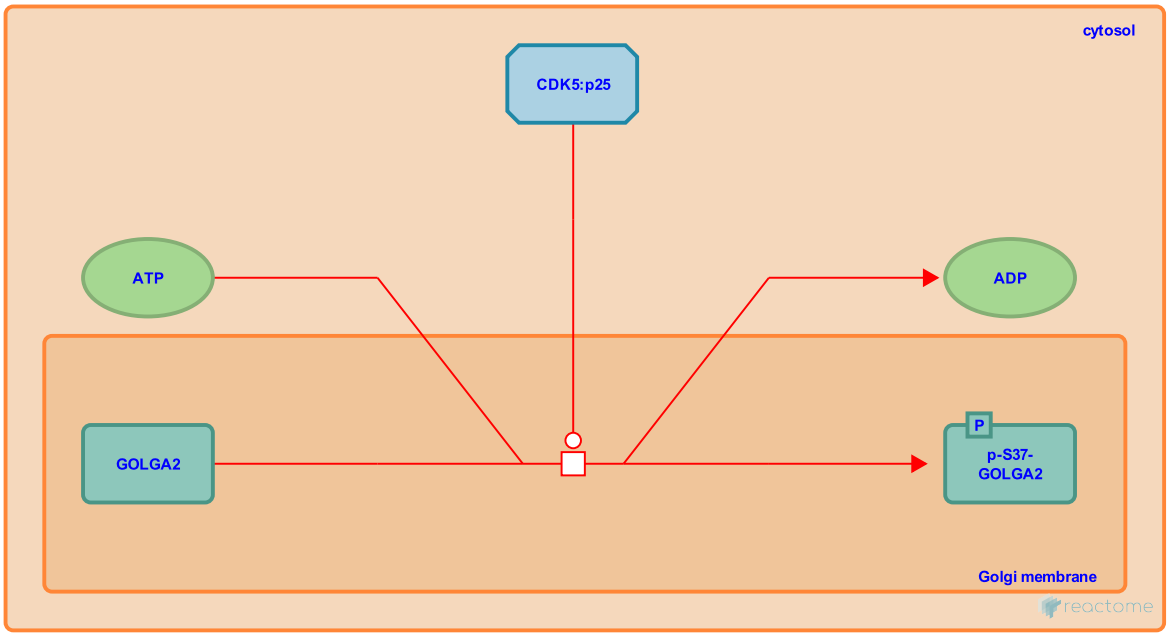
Stable identifier: R-HSA-8868260

Type: transition

Compartments: Golgi membrane, cytosol

Diseases: Alzheimer's disease

Inferred from: Cdk5:p25 phosphorylates Golga2 (Mus musculus)



Golgi fragmentation is observed in neurodegenerative diseases, including Alzheimer's disease. The underlying mechanism, based on a mouse AD model, is the phosphorylation of the Golgi membrane protein GOLGA2 (GM130) by the CDK5:p25 complex. CDK5:p25 phosphorylates GOLGA2 (GM130) on a conserved residue S37, phosphorylated by CDK1 in mitotic prophase (Lowe et al. 1998), triggering Golgi apparatus disassembly in Alzheimer's disease (Sun et al. 2008). Please note that S37 of GOLGA2 is sometimes labeled as S25 in the literature because the recombinant Golga2 construct used in the original study of mitotic Golgi fragmentation (Lowe et al. 1998) lacked 12 N-terminal amino acids of Golga2.

Preceded by: CDK5 binds p25

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5:p25 translocates to the nucleus ↗

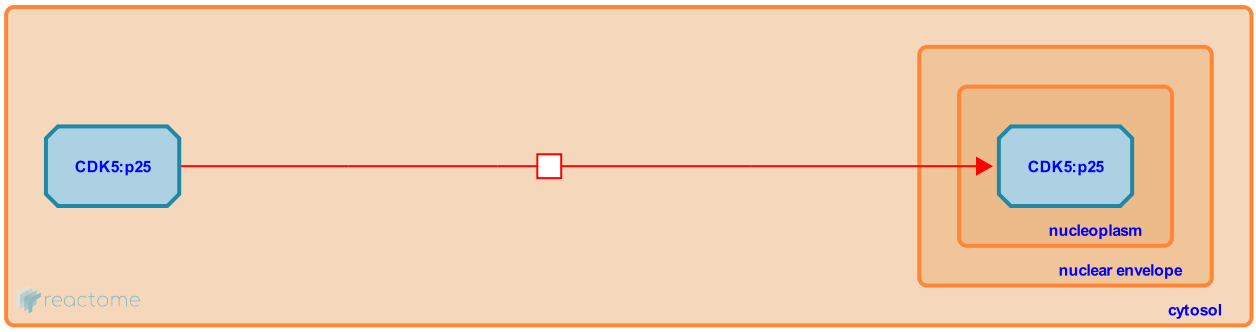
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8863587

Type: transition

Compartments: cytosol, nucleoplasm

Diseases: Alzheimer's disease



The complex of CDK5 and p25 can translocate to the nucleus (Patrick et al. 1999). Nuclear envelope fragmentation, initiated by CDK5:p25-mediate phosphorylation of lamin A and B1, increases access of the CDK5:p25 complex to nuclear proteins (Chang et al. 2011).

Preceded by: CDK5 binds p25

Followed by: CDK5:p25 phosphorylates lamin A, CDK5:p25 phosphorylates lamin B1, p25-bound CDK5 phosphorylates CDC25A

Literature references

Patrick, GN., Zukerberg, L., Nikolic, M., de la Monte, S., Dikkes, P., Tsai, LH. (1999). Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. *Nature, 402*, 615-22. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5:p25 phosphorylates lamin A ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

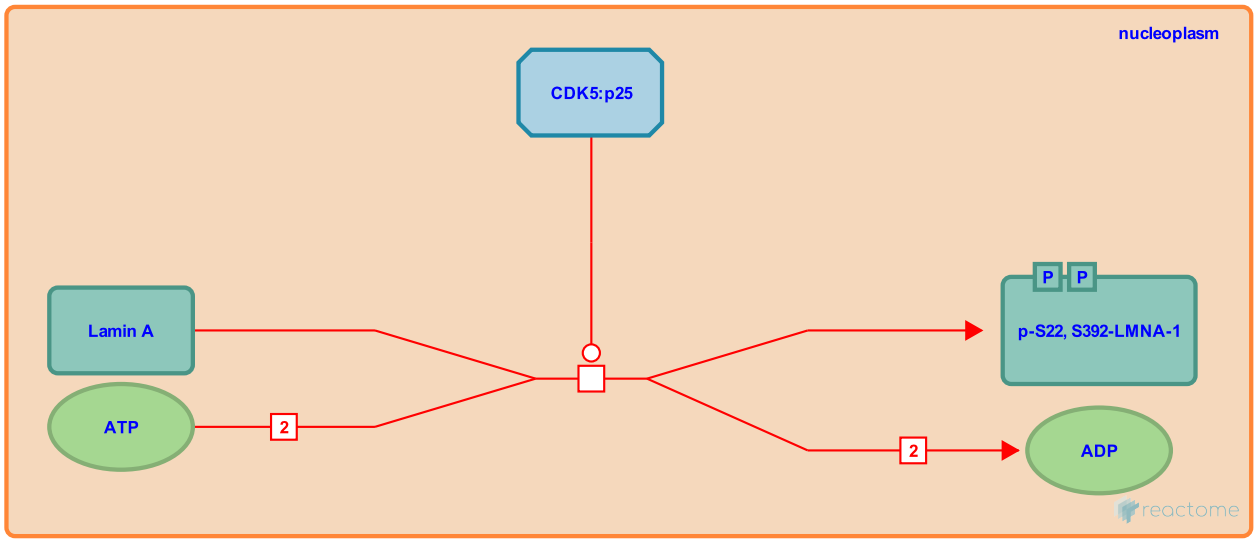
Stable identifier: R-HSA-8868344

Type: transition

Compartments: nucleoplasm

Diseases: Alzheimer's disease

Inferred from: Cdk5:p25 phosphorylates lamin A (Mus musculus)



Alzheimer's disease (AD), like many other neurodegenerative diseases, is characterized by nuclear envelope fragmentation. Based on a mouse AD model, nuclear fragmentation is initiated by phosphorylation of nuclear lamins by p25-activated CDK5. The CDK5:p25 complex phosphorylates lamin A (LMNA-1) at serine residues S22 and S392, with S392 being the major CDK5 target site. Nuclear envelope fragmentation increases access of the CDK5:p25 complex to nuclear proteins and precedes neuronal death (Chang et al. 2011).

Preceded by: CDK5:p25 translocates to the nucleus

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5:p25 phosphorylates lamin B1 ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

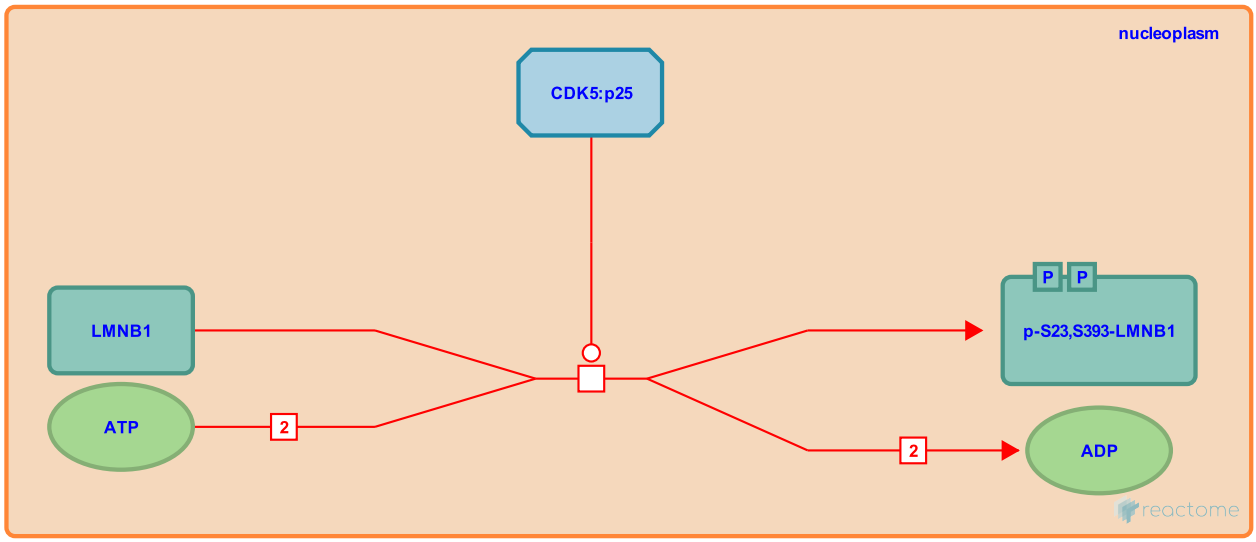
Stable identifier: R-HSA-8868340

Type: transition

Compartments: nucleoplasm

Diseases: Alzheimer's disease

Inferred from: Cdk5:p25 phosphorylates lamin B1 (Mus musculus)



Alzheimer's disease (AD), like many other neurodegenerative diseases, is characterized by nuclear envelope fragmentation. Based on a mouse AD model, nuclear fragmentation is initiated by phosphorylation of nuclear lamins by p25-activated CDK5. The CDK5:p25 complex phosphorylates lamin B1 (LMNB1) at serine residues S23 and S393. Nuclear envelope fragmentation increases access of the CDK5:p25 complex to nuclear proteins and precedes neuronal death (Chang et al. 2011).

Preceded by: CDK5:p25 translocates to the nucleus

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5:p25 phosphorylates PRDX1 ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

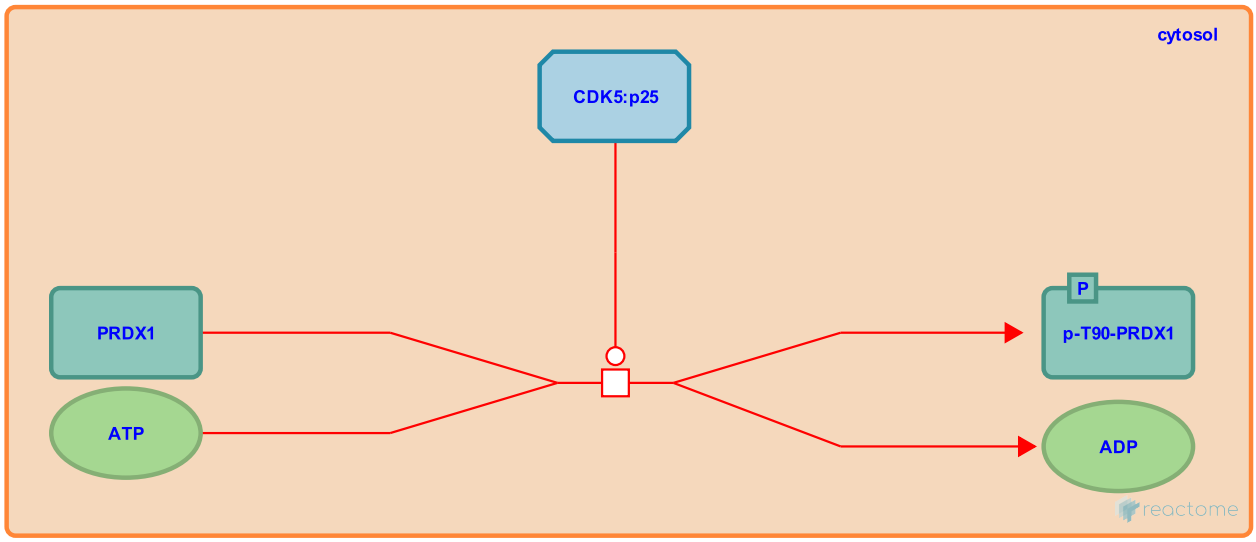
Stable identifier: R-HSA-8868567

Type: transition

Compartments: cytosol

Diseases: Alzheimer's disease

Inferred from: Cdk5:p25 phosphorylates Prdx1 (Mus musculus)



Oxidative stress, manifested through accumulation of reactive oxygen species in the cell, is one of the hallmarks of Alzheimer's disease. Based on mouse model studies, CDK5, aberrantly activated by binding to p25, phosphorylates the peroxide reductase PRDX1 on a conserved threonine residue T90, thus inactivating it and contributing to ROS accumulation (Sun et al. 2008).

Preceded by: CDK5 binds p25

Literature references

Sun, KH., de Pablo, Y., Vincent, F., Shah, K. (2008). Deregulated Cdk5 promotes oxidative stress and mitochondrial dysfunction. *J. Neurochem., 107*, 265-78. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5:p25 phosphorylates PRDX2 ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

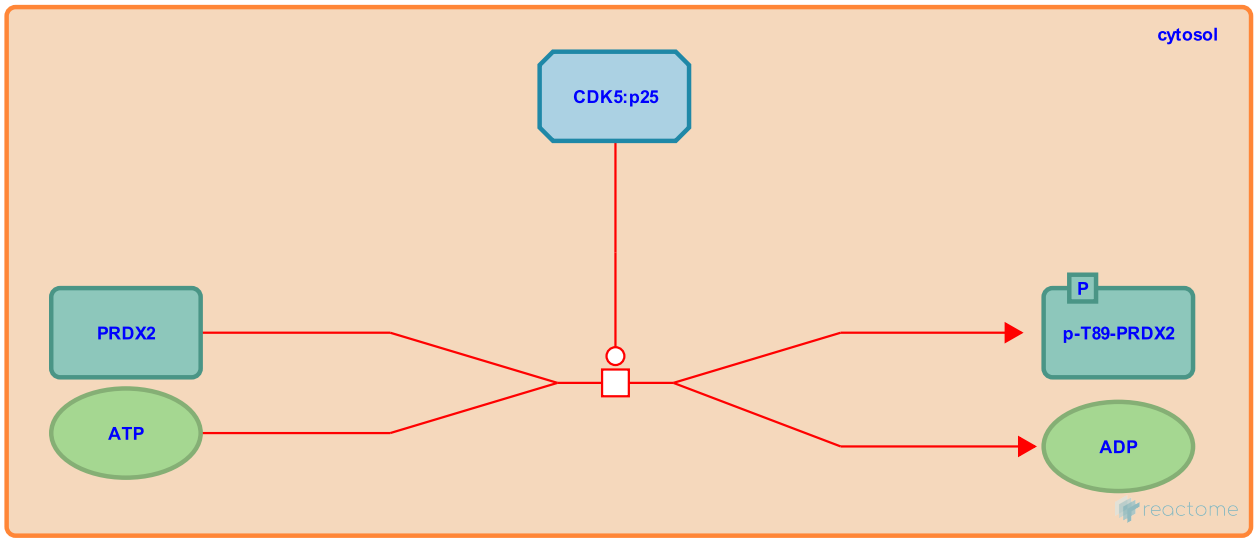
Stable identifier: R-HSA-8868573

Type: transition

Compartments: cytosol

Diseases: Alzheimer's disease

Inferred from: Cdk5:p25 phosphorylates Prdx2 (Mus musculus)



Oxidative stress, manifested through accumulation of reactive oxygen species in the cell, is one of the hallmarks of Alzheimer's disease. Based on mouse model studies, CDK5, aberrantly activated by binding to p25, phosphorylates the peroxide reductase PRDX2 on a conserved threonine residue T89, thus inactivating it and contributing to ROS accumulation (Sun et al. 2008).

Preceded by: CDK5 binds p25

Literature references

Sun, KH., de Pablo, Y., Vincent, F., Shah, K. (2008). Deregulated Cdk5 promotes oxidative stress and mitochondrial dysfunction. *J. Neurochem., 107*, 265-78. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-10	Edited	Orlic-Milacic, M.

CDK5:p25 phosphorylates JUN ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

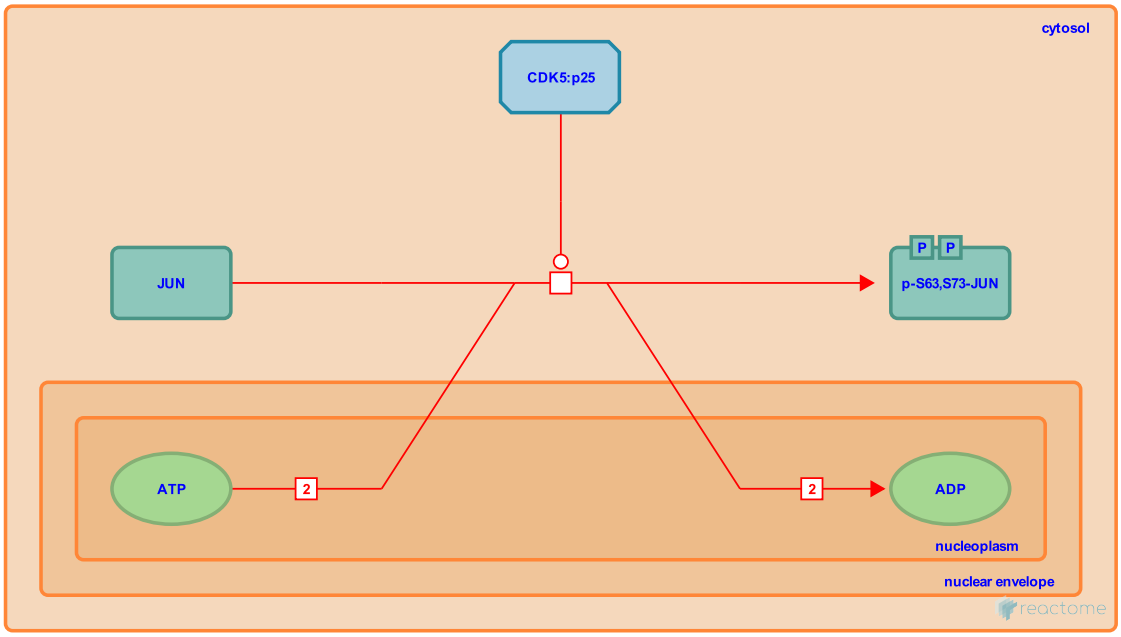
Stable identifier: R-HSA-8868666

Type: transition

Compartments: cytosol

Diseases: Alzheimer's disease

Inferred from: Cdk5:p25 phosphorylates Jun (Mus musculus)



Based on mouse model studies, the JUN transcription factor undergoes biphasic activation in Alzheimer's disease. JUN is phosphorylated directly by p25-bound CDK5 at serine residues S63 and S73. CDK5:p25-mediated increase in the level of reactive oxygen species (ROS) triggers activation of JNK kinases (MAPK8, MAPK9, MAPK10), which phosphorylate JUN at S63 and S73 at a later time point (Sun et al. 2009).

Aberrant activation of CDK5 by p25 binding also triggers activation of MKK6 (MAP2K6), a p38 MAP kinase. Levels of phosphorylated MAP2K6 are increased in Alzheimer's disease. Activation of p38 MAP kinase(s) results in increased JUN expression (Chang et al. 2010).

Editions

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CDK5:p25 phosphorylates FOXO3 ↗

Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

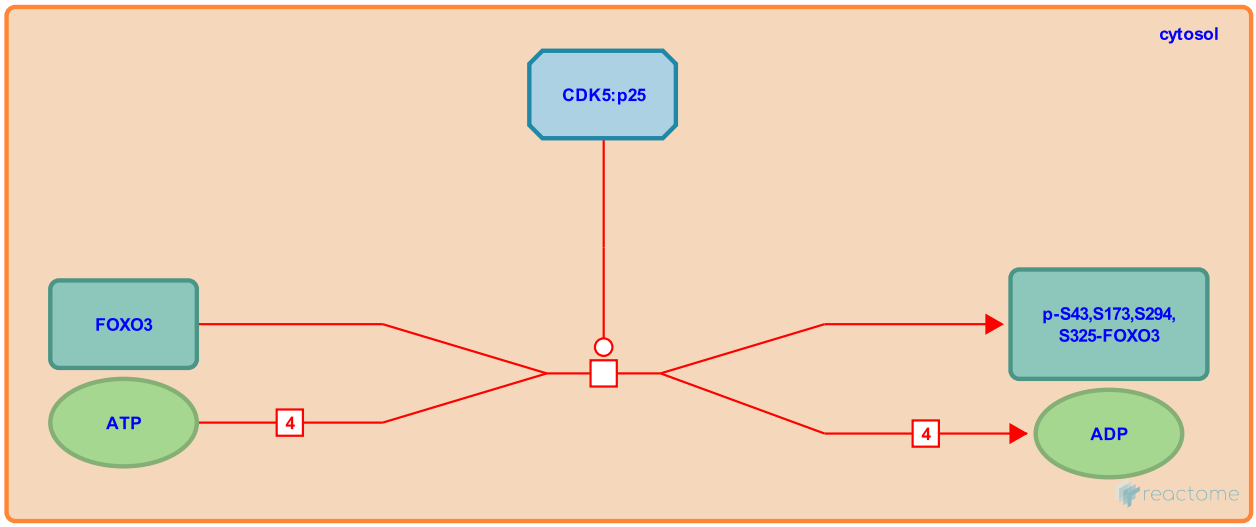
Stable identifier: R-HSA-8870558

Type: transition

Compartments: cytosol

Diseases: Alzheimer's disease

Inferred from: Cdk5:p25 phosphorylates FOXO3 (Homo sapiens)



CDK5, aberrantly activated by binding to p25, phosphorylates transcription factor FOXO3 on serine residues S43, S173, S294 and S325 (Shi et al. 2016).

Preceded by: CDK5 binds p25

Followed by: Phosphorylated FOXO3 translocates to the nucleus

Literature references

Shi, C., Viccaro, K., Lee, HG., Shah, K. (2016). Cdk5-FOXO3a axis: initially neuroprotective, eventually neurodegenerative in Alzheimer's disease models. *J. Cell. Sci.*. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-11	Edited	Orlic-Milacic, M.

Phosphorylated FOXO3 translocates to the nucleus ↗

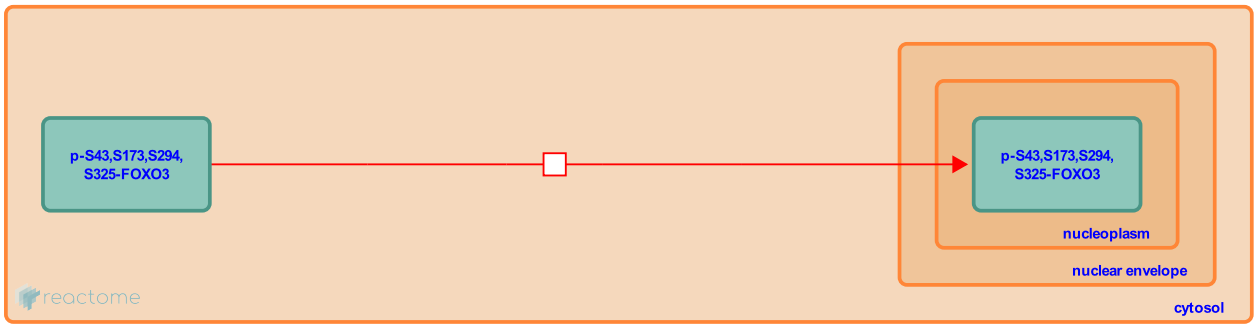
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8870628

Type: transition

Compartments: cytosol, nucleoplasm

Diseases: Alzheimer's disease



CDK5-mediated phosphorylation of the transcription factor FOXO3 promotes translocation of FOXO3 from the cytosol to the nucleus (Shi et al. 2016).

Preceded by: CDK5:p25 phosphorylates FOXO3

Followed by: BCL2L11 (BIM) gene expression, APP gene expression, FASLG (FasL) gene expression, SOD2 (MnSOD) gene expression

Literature references

Shi, C., Viccaro, K., Lee, HG., Shah, K. (2016). Cdk5-FOXO3a axis: initially neuroprotective, eventually neurodegenerative in Alzheimer's disease models. *J. Cell. Sci.*. ↗

Editions

2016-02-23	Authored	Shah, K.
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BCL2L11 (BIM) gene expression ↗

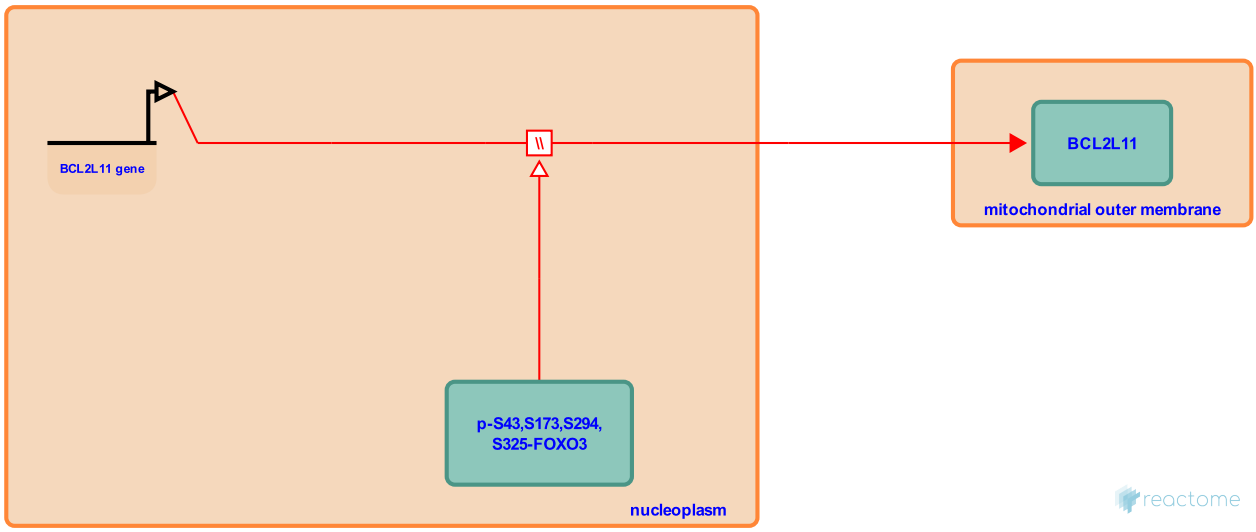
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8870686

Type: omitted

Compartments: nucleoplasm, mitochondrial outer membrane

Diseases: Alzheimer's disease



Transcription of the pro-apoptotic BCL2L11 (BIM) gene is stimulated by FOXO3 downstream of CDK5-mediated FOXO3 phosphorylation (Shi et al. 2016).

Preceded by: Phosphorylated FOXO3 translocates to the nucleus

Literature references

Shi, C., Viccaro, K., Lee, HG., Shah, K. (2016). Cdk5-FOXO3a axis: initially neuroprotective, eventually neurodegenerative in Alzheimer's disease models. *J. Cell. Sci.*. ↗

Editions

2016-02-23	Authored	Shah, K.
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FASLG (FasL) gene expression ↗

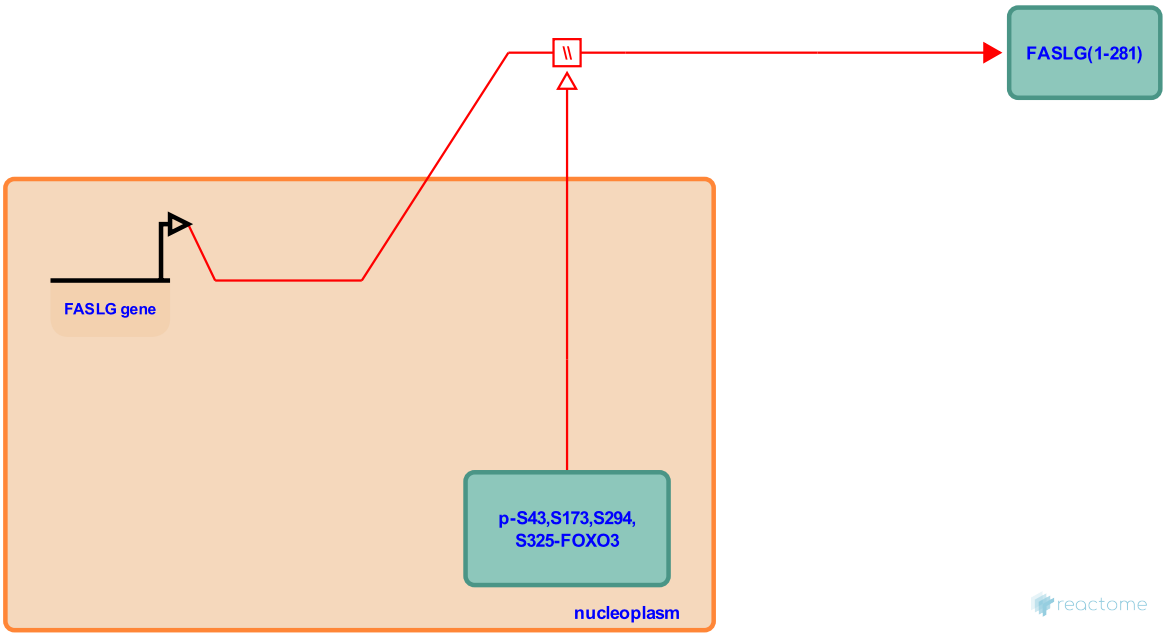
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8870698

Type: omitted

Compartments: extracellular region, nucleoplasm

Diseases: Alzheimer's disease



Transcription of the FASLG (FasL) gene, encoding the death receptor ligand, is stimulated by FOXO3 phosphorylated by aberrantly activated CDK5 (Shi et al. 2016).

Preceded by: Phosphorylated FOXO3 translocates to the nucleus

Literature references

Shi, C., Viccaro, K., Lee, HG., Shah, K. (2016). Cdk5-FOXO3a axis: initially neuroprotective, eventually neurodegenerative in Alzheimer's disease models. *J. Cell. Sci.*. ↗

Editions

2016-02-23	Authored	Shah, K.
2016-05-11	Edited	Orlic-Milacic, M.

SOD2 (MnSOD) gene expression ↗

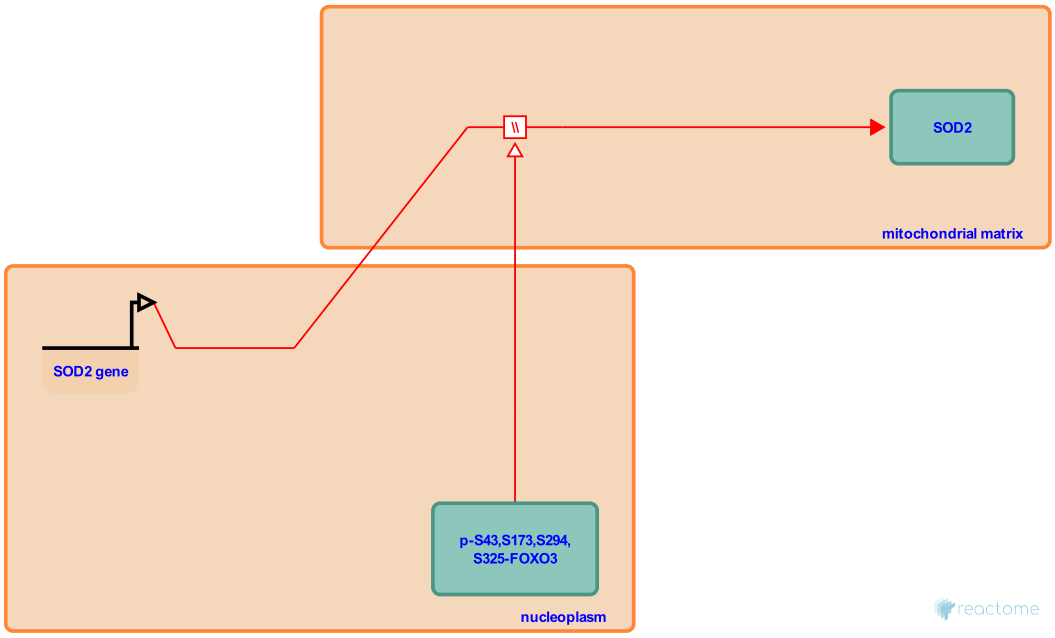
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8870703

Type: omitted

Compartments: mitochondrial matrix, nucleoplasm

Diseases: Alzheimer's disease



Transcription of the SOD2 (MnSOD) gene, encoding mitochondrial superoxide dismutase, is stimulated by FOXO3 downstream of aberrantly activated CDK5 (Shi et al. 2016).

Preceded by: Phosphorylated FOXO3 translocates to the nucleus

Literature references

Shi, C., Viccaro, K., Lee, HG., Shah, K. (2016). Cdk5-FOXO3a axis: initially neuroprotective, eventually neurodegenerative in Alzheimer's disease models. *J. Cell. Sci.*. ↗

Editions

2016-02-23	Authored	Shah, K.
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APP gene expression ↗

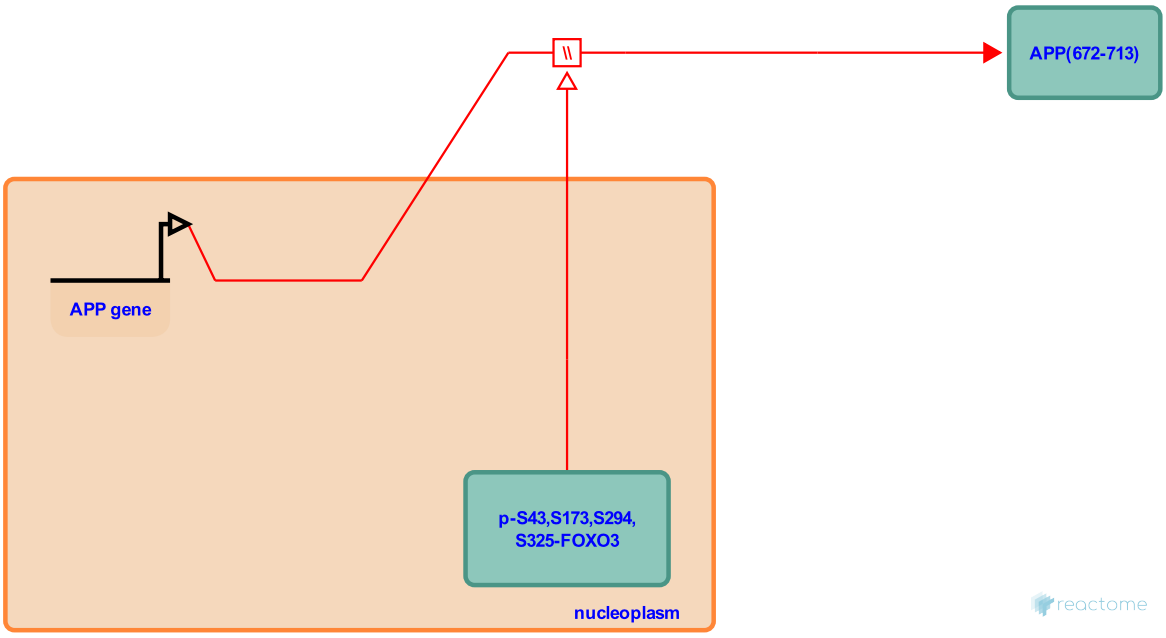
Location: Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models

Stable identifier: R-HSA-8870710

Type: omitted

Compartments: extracellular region, nucleoplasm

Diseases: Alzheimer's disease



Transcription of the APP gene is increased by FOXO3, downstream of FOXO3 phosphorylation by aberrantly activated CDK5 (Shi et al. 2016).

Preceded by: Phosphorylated FOXO3 translocates to the nucleus

Literature references

Shi, C., Viccaro, K., Lee, HG., Shah, K. (2016). Cdk5-FOXO3a axis: initially neuroprotective, eventually neurodegenerative in Alzheimer's disease models. *J. Cell. Sci.*. ↗

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