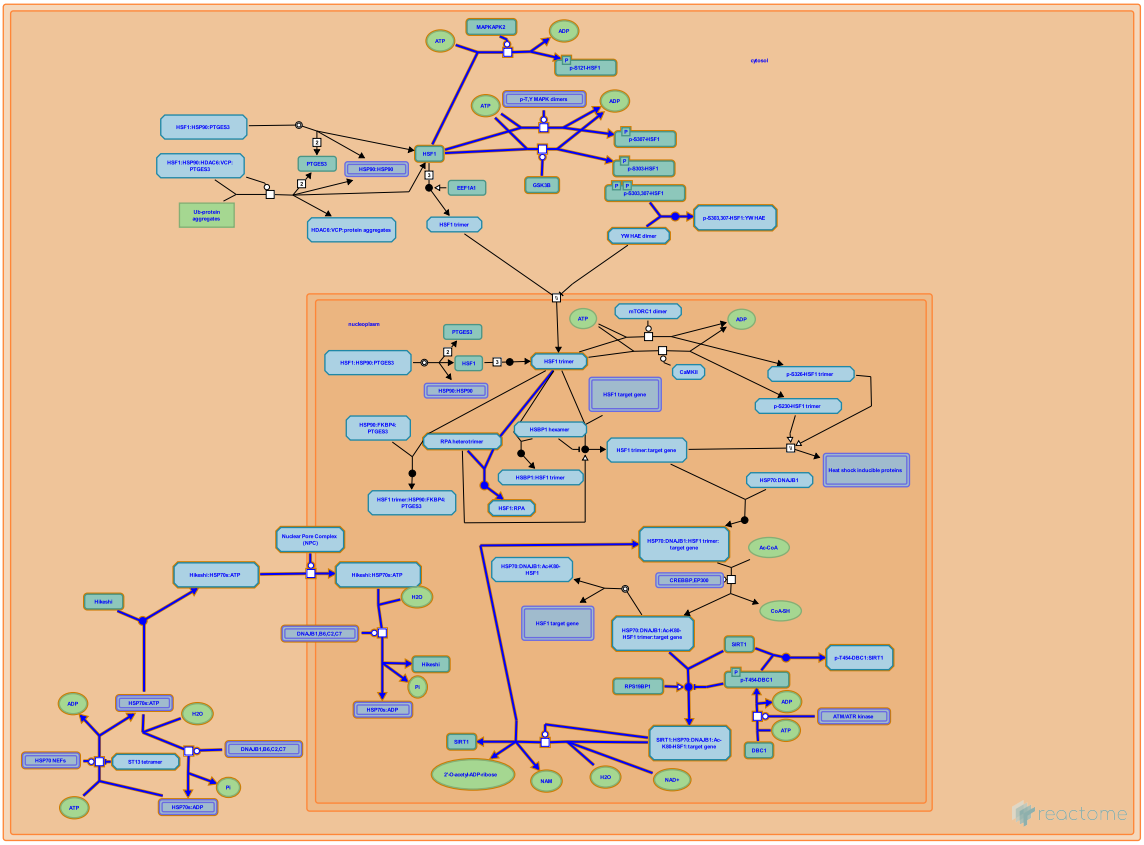
Regulation of HSF1-mediated heat shock response



D'Eustachio, P., Jassal, B., Pani, B., Shamovsky, V.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

03/05/2024

Introduction

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

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

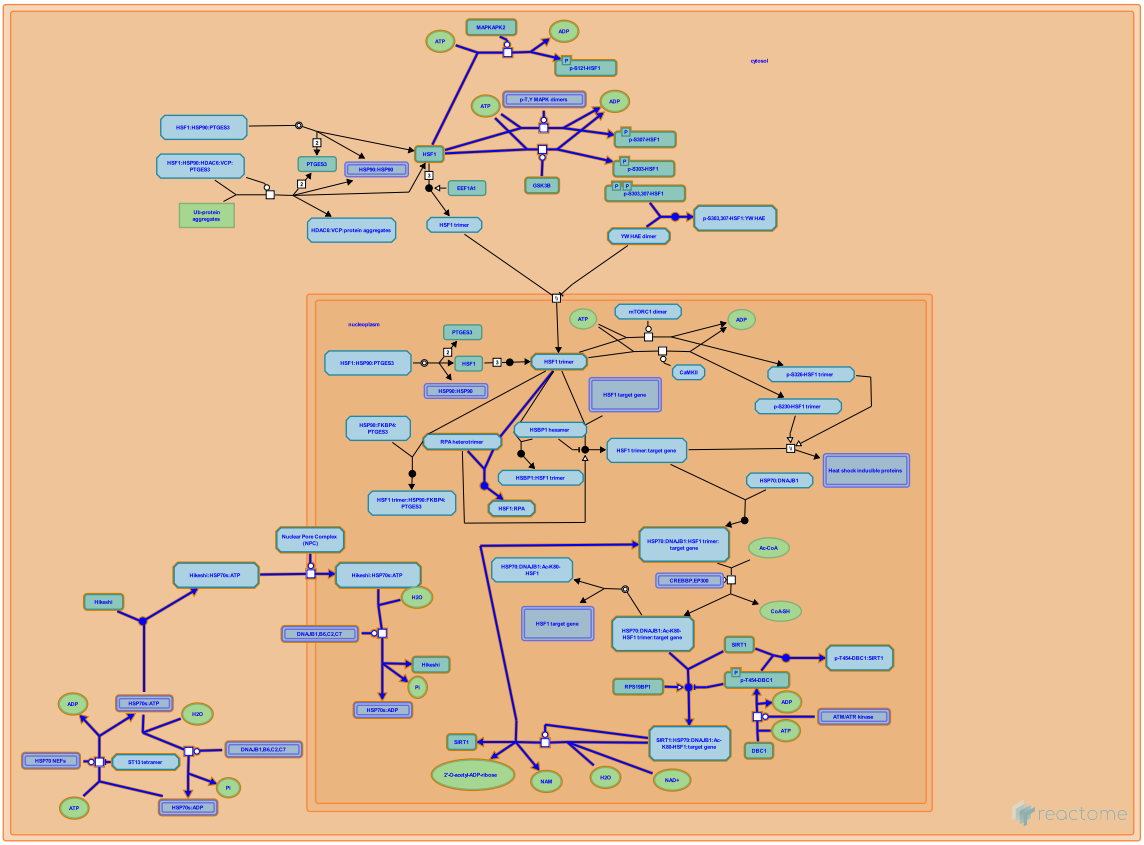
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Regulation of HSF1-mediated heat shock response ↗

Stable identifier: R-HSA-3371453



The ability of HSF1 to respond to cellular stresses is under negative regulation by chaperones, modulation of nucleocytoplasmic shuttling, post-translational modifications and transition from monomeric to trimeric state.

Literature references

Rungger, D., Voellmy, R., Zuo, J. (1995). Multiple layers of regulation of human heat shock transcription factor 1. *Mol. Cell. Biol., 15*, 4319-30. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

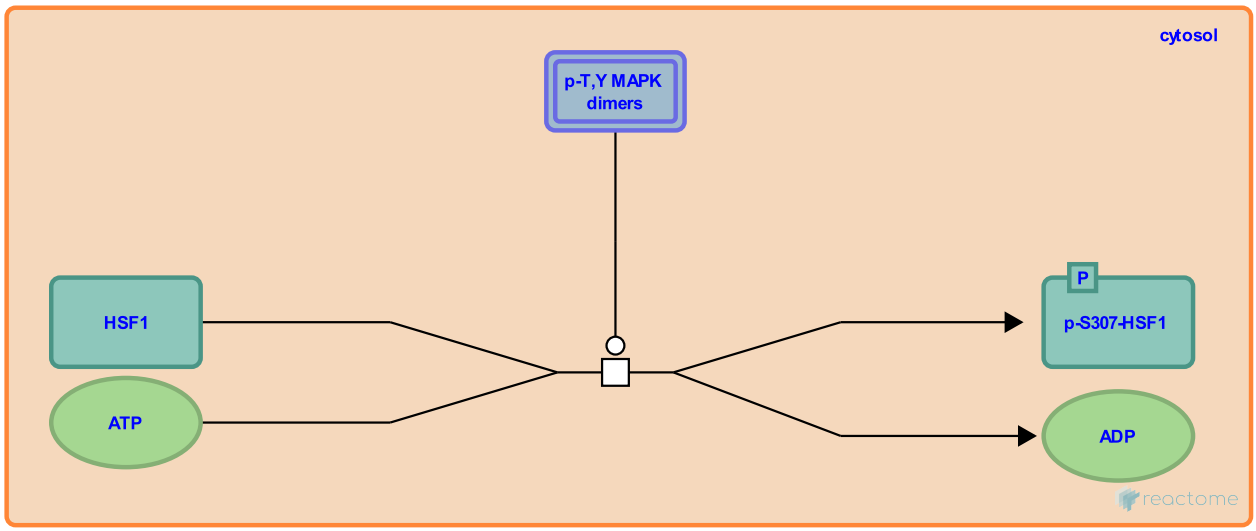
Constitutive phosphorylation by pERK1/2

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-3371531

Type: transition

Compartments: cytosol



Constitutive phosphorylation at Ser307 was shown to inhibit HSF1 transcriptional activity under normal temperatures. Substitution of Ser307 with alanine derepresses the transactivation domain such that the S307A mutant showed increased transcriptional activity in human and mouse cells (Knauf U et al. 1996; Kline MP & Morimoto RI 1997).
HSF1-ERK association was shown to promote ERK activity in human HeLa, acute monocytic leukemia THP1 and metastatic cutaneous SCC7 cells resulting in phosphorylation of HSF1 on Ser307 (Chu B et al. 1996; Wang X et al. 2004). This phosphorylation in turn promoted HSF1 association with YWHAE (14-3-3 epsilon), which may be involved in the attenuation of HSF1 activity during recovery and leads to accelerated cytoplasmic localization of HSF1 (Wang X et al. 2003, 2004).

Followed by: p-S303,307-HSF1 binds YWHAE (14-3-3)

Literature references

Kyriakis, J., Kingston, RE., Knauf, U., Newton, EM. (1996). Repression of human heat shock factor 1 activity at control temperature by phosphorylation. *Genes Dev., 10,* 2782-93.

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

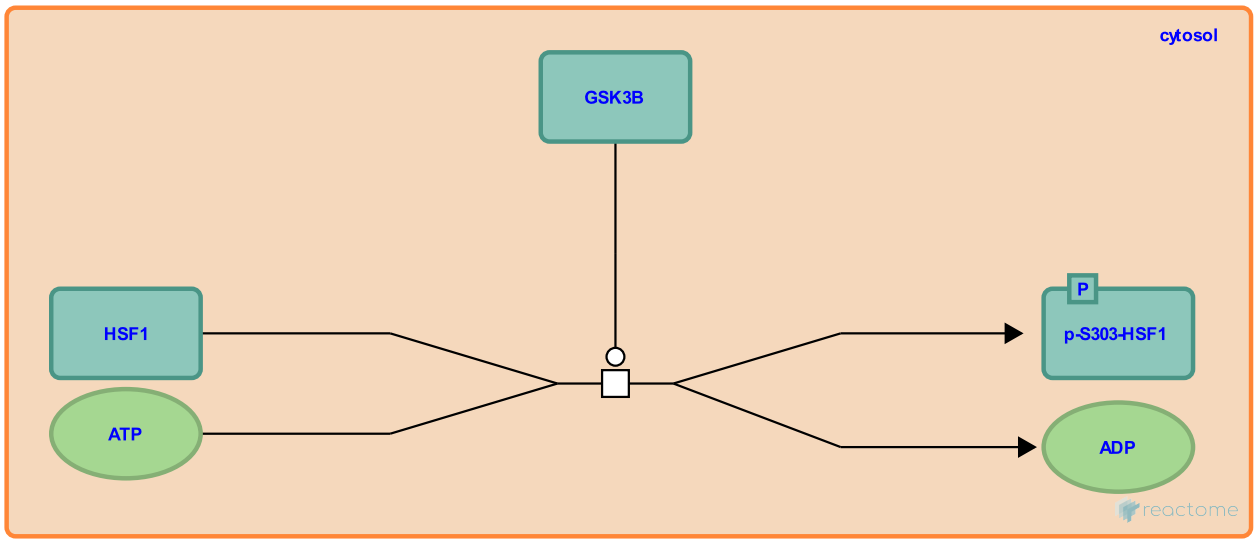
Constitutive phosphorylation by GSK3 ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-3371435

Type: transition

Compartments: cytosol



Constitutive phosphorylation at Ser303 within the regulatory domain of HSF1 was shown to inhibit its transcriptional activity under normal temperatures. Substitution of Ser303 with alanine derepresses the transactivation domain such that the S303A mutant showed increased transcriptional activity in human and mouse cells (Knauf U et al. 1996; Kline MP & Morimoto RI 1997). Phosphorylation of HSF1 at Ser303 was mediated by glycogen synthase kinase 3 (GSK3) activity in human acute monocytic leukemia THP1 cells and mouse embryonic fibroblast NIH 3T3 cells (Chu B et al. 1996, 1998). However, the other group showed that GSK3 inhibits HSF1 activity in HeLa cells through a mechanism that is independent of Ser303 phosphorylation, thus suggesting that Ser303 may be phosphorylated by multiple MAPKs (Batista?Nascimento L et al. 2011). The phosphorylation at Ser303 in turn promoted HSF1 association with YWHAE (14-3-3 epsilon), which may be involved in the attenuation of HSF1 activity during recovery leading to accelerated cytoplasmic localization of HSF1 (Wang X et al. 2003, 2004).In addition, stress stimulated human K562 erythroleukemia cells showed enhanced level of sumoylation in the HSF1 regulatory domain at Lys298, which was positively regulated by Ser303 phosphorylation (Hietakangas V et al. 2003).

Followed by: p-S303,307-HSF1 binds YWHAE (14-3-3)

Literature references

Kyriakis, J., Kingston, RE., Knauf, U., Newton, EM. (1996). Repression of human heat shock factor 1 activity at control temperature by phosphorylation. *Genes Dev., 10,* 2782-93. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

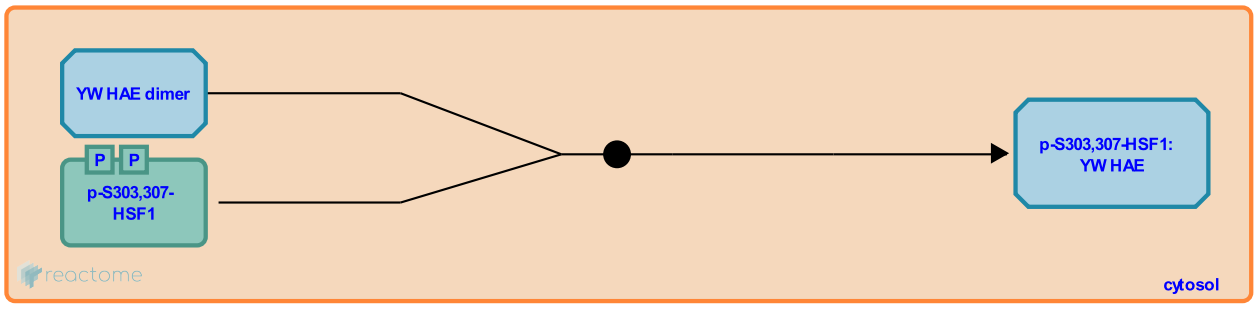
p-S303,307-HSF1 binds YWHAE (14-3-3)

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-4793925

Type: binding

Compartments: cytosol



YWHAE (14-3-3epsilon) was found to bind directly to HSF1 and that binding required serine phosphorylation at Ser303 and Ser307 and, moreover, the strongest binding was detected when both residues were phosphorylated.

Preceded by: Constitutive phosphorylation by GSK3, Constitutive phosphorylation by pERK1/2

Literature references

Grammatikakis, N., Wang, X., Stevenson, MA., Calderwood, SK., Siganou, A. (2004). Interactions between extracellular signal-regulated protein kinase 1, 14-3-3epsilon, and heat shock factor 1 during stress. *J. Biol. Chem., 279*, 49460-9.

Grammatikakis, N., Wang, X., Calderwood, SK., Siganou, A. (2003). Regulation of molecular chaperone gene transcription involves the serine phosphorylation, 14-3-3 epsilon binding, and cytoplasmic sequestration of heat shock factor 1. *Mol. Cell. Biol., 23*, 6013-26.

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

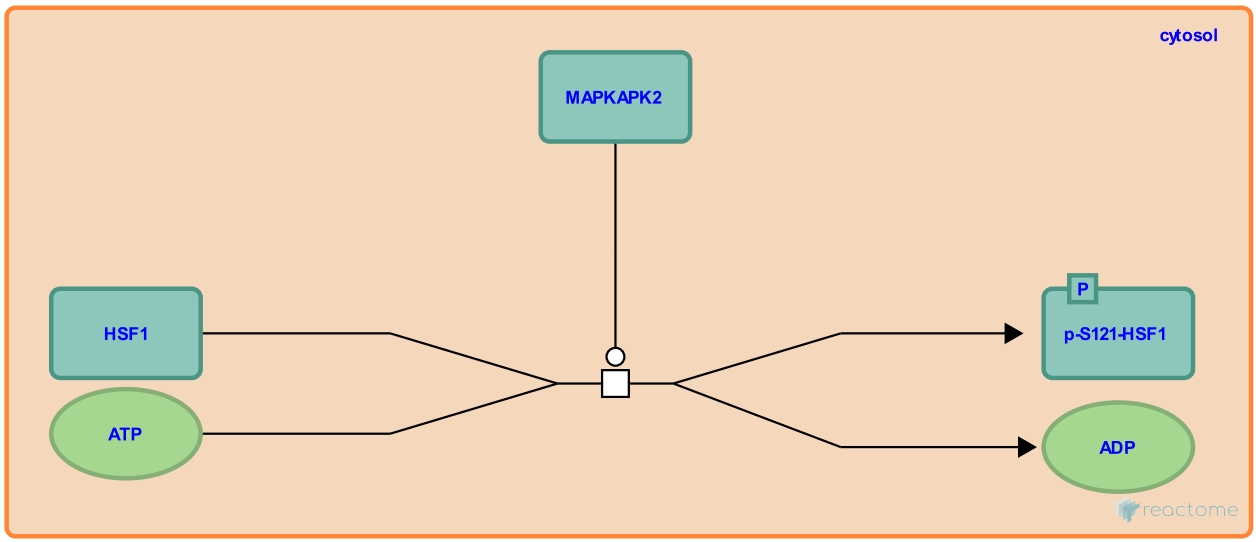
MAPKAPK2 phosphorylates HSF1 ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-4793911

Type: transition

Compartments: cytosol



Phosphorylation on Ser-121 inhibits transactivation and promotes HSP90 binding

Literature references

Wang, X., Zhao, MJ., Gaestel, M., Zhong, R., Calderwood, SK., Khaleque, MA. (2006). Phosphorylation of HSF1 by MAPK-activated protein kinase 2 on serine 121, inhibits transcriptional activity and promotes HSP90 binding. *J. Biol. Chem., 281*, 782-91. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

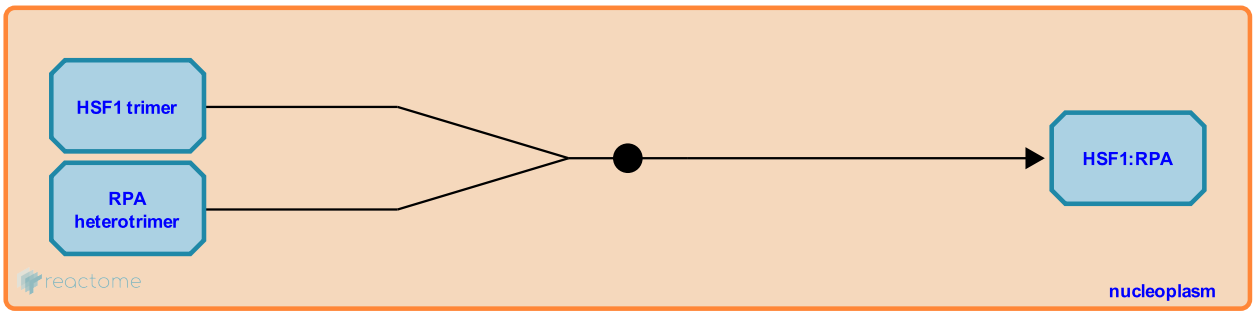
RPA1 binds HSF1 ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-5333051

Type: binding

Compartments: nucleoplasm



Replication protein A (RPA) is a heterotrimeric, single-strand DNA-binding protein required for DNA metabolism, including DNA replication, repair, and recombination. The physical interaction between the wing motif of human HSF1 and RPA1 was found to provide HSF1 access to nucleosomal DNA, which is important for both basal and inducible gene expression. This access lead to preloading of RNA polymerase II and opened the chromatin structure by recruiting a histone chaperone FACT (Fujimoto M et al. 2012).

Literature references

Takii, R., Natsume, T., Fujimoto, M., Nakai, A., Hayashida, N., Tan, K. et al. (2012). RPA assists HSF1 access to nucleosomal DNA by recruiting histone chaperone FACT. *Mol. Cell, 48*, 182-94. ↗

Editions

2014-02-17	Reviewed	Pani, B.
2014-02-18	Authored	Shamovsky, V.
2014-02-19	Edited	Shamovsky, V.

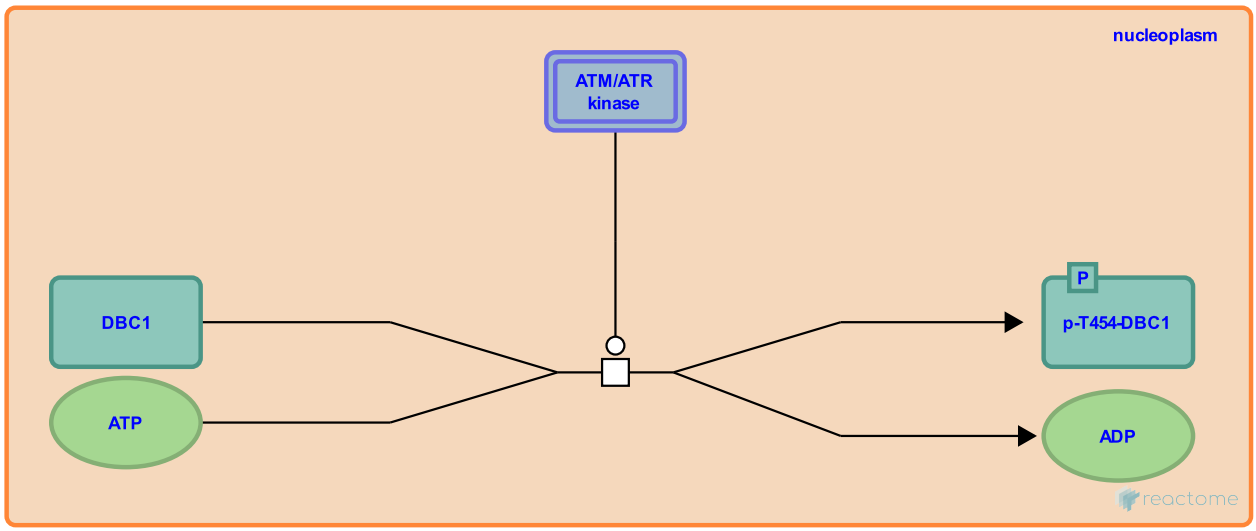
DBC1 is phosphorylated by ATM/ART ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-3371567

Type: transition

Compartments: nucleoplasm



The stress-induced DBC1-SIRT1 interaction required the ATM/ATR-dependent phosphorylation of DBC1 at Thr454 (Yuan J et al. 2012; Zannini L et al. 2012).

Followed by: DBC1 binds SIRT1

Literature references

Liu, T., Lou, Z., Yuan, J., Luo, K. (2012). Regulation of SIRT1 activity by genotoxic stress. *Genes Dev., 26*, 791-6. ↗

Delia, D., Zannini, L., Kim, JE., Buscemi, G., Fontanella, E. (2012). DBC1 phosphorylation by ATM/ATR inhibits SIRT1 deacetylase in response to DNA damage. *J Mol Cell Biol, 4*, 294-303. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

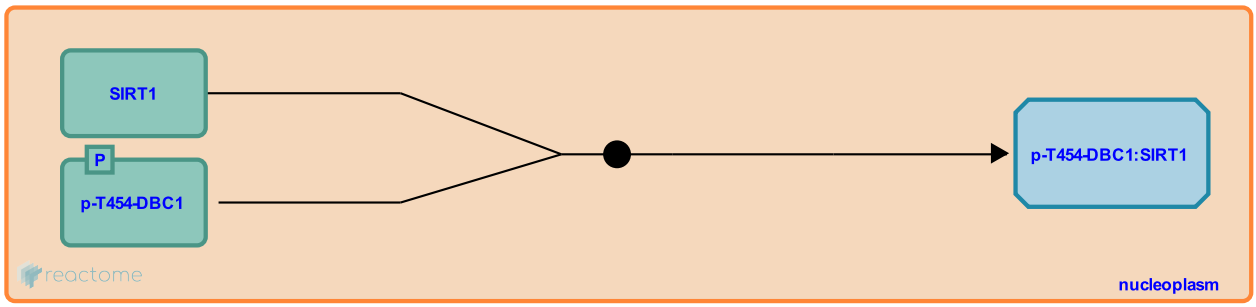
DBC1 binds SIRT1 ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-3371537

Type: binding

Compartments: nucleoplasm



SIRT1 is a (NAD+)-dependent deacetylase that was reported to regulate a number of target proteins, including histones, p53, HSF1, and NF-kappaB (Vaziri H et al. 2001; Yeung F et al. 2004; Westerheide SD et al. 2009). The substrate binding to SIRT1 can be interrupted by DBC1 (deleted in breast cancer 1), which was found to associate with the catalytic core domain of SIRT1 (Zhao W et al. 2008; Kim JE et al. 2008). DBC1 inhibited NAD-dependent deacetylase activity of SIRT1 in response to DNA damage or oxidative stress in human and mouse cells (Zhao W et al. 2008; Kim JE et al. 2008; Yuan J et al. 2012).

The stress-induced DBC1-SIRT1 interaction required the ATM/ATR-dependent phosphorylation of DBC1 at Thr454 (Yuan J et al. 2012; Zannini L et al. 2012). Furthermore. the DBC1:SIRT1 complex is a dynamic formation, which was shown to be regulated by manipulating the SIRT1 phosphorylation status via cAMP/PKA and AMP-activated protein kinase (AMPK) activity (Nin V et al 2012). PKA has been also implicated in the regulation of HSF1-mediated responses, however not all inducing stimulies led to PKA-HSF1 association (Murshid A et al. 2010).

Preceded by: DBC1 is phosphorylated by ATM/ART

Literature references

Lou, Z., Kim, JE., Chen, J. (2008). DBC1 is a negative regulator of SIRT1. *Nature, 451*, 583-6. ↗

Gu, W., Kruse, JP., Jung, SY., Tang, Y., Zhao, W., Qin, J. (2008). Negative regulation of the deacetylase SIRT1 by DBC1 . *Nature, 451*, 587-90. ↗

Mendez, JE., Brunquell, J., Nguyen, K., Westerheide, SD., Raynes, R., Pombier, KM. (2013). The SIRT1 modulators AROS and DBC1 regulate HSF1 activity and the heat shock response. *PLoS ONE, 8*, e54364. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

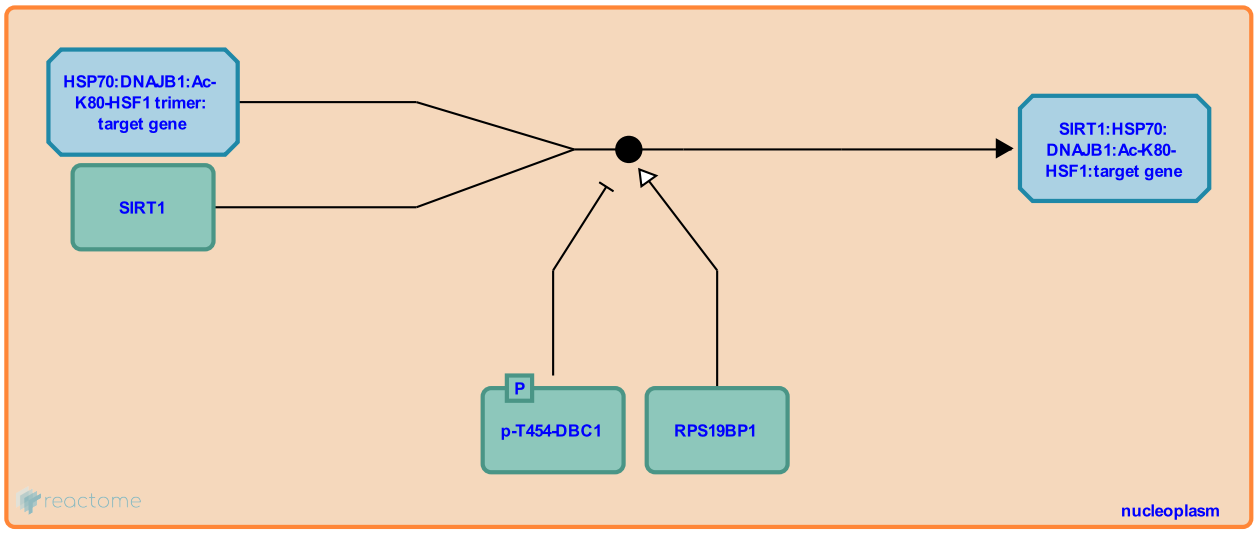
SIRT1 binds to HSF1

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-3371518

Type: binding

Compartments: nucleoplasm



Surtuin 1 (SIRT1) has been shown to bind HSF1 and to function as a regulator of HSF1 DNA binding activity by controling the acetylation status of HSF1 (Westerheide SD et al 2009). SIRT1 mediates NAD(+)-dependent protein deacetylation.

Followed by: SIRT1 deacetylates HSF1

Literature references

Mendez, JE., Brunquell, J., Nguyen, K., Westerheide, SD., Raynes, R., Pombier, KM. (2013). The SIRT1 modulators AROS and DBC1 regulate HSF1 activity and the heat shock response. *PLoS ONE, 8*, e54364.

Sistonen, L., Morimoto, RI., Westerheide, SD., Anckar, J., Stevens, SM. (2009). Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. *Science, 323*, 1063-6.

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

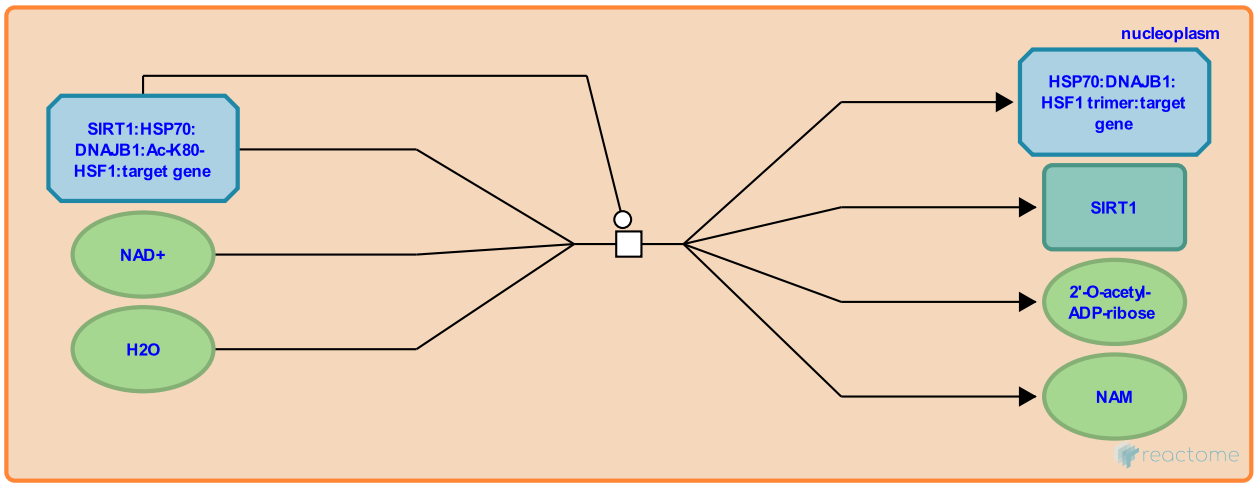
SIRT1 deacetylates HSF1 ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-3371467

Type: transition

Compartments: nucleoplasm



Sirtuin 1 (SIRT1) functions as a NAD(+)-dependent deacetylase, which regulates the heat shock response through deacetylation of HSF1 at Lys80. The acetylation at Lys80, which is located within DNA binding domain of HSF1 disrupts HSF1 DNA-binding ability. SIRT1-mediated stress-inducible regulation of HSF1 results in prolonged HSF1 binding to the heat shock promoter of hsp70 gene. The mechanism of the enzymatic reaction which couples NAD(+) hydrolysis with lysine deacetylation in the presence of acetylated peptide is described by several groups (Landry J et al. 2000; Sauve AA et al. 2001)

Preceded by: SIRT1 binds to HSF1

Literature references

Zheng, W., Pang, Y., Hirsch, BM., Jamonnak, N. (2010). Substrate specificity of SIRT1-catalyzed lysine Nepsilon-deacetylation reaction probed with the side chain modified Nepsilon-acetyl-lysine analogs. *Bioorg. Chem., 38*, 17-25. ↗

Celic, I., Avalos, J., Boeke, JD., Deng, H., Schramm, VL., Sauve, AA. (2001). Chemistry of gene silencing: the mechanism of NAD+-dependent deacetylation reactions. *Biochemistry, 40*, 15456-63. ↗

Mendez, JE., Brunquell, J., Nguyen, K., Westerheide, SD., Raynes, R., Pombier, KM. (2013). The SIRT1 modulators AROS and DBC1 regulate HSF1 activity and the heat shock response. *PLoS ONE, 8*, e54364. ↗

Sistonen, L., Morimoto, RI., Westerheide, SD., Anckar, J., Stevens, SM. (2009). Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. *Science, 323*, 1063-6. ↗

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

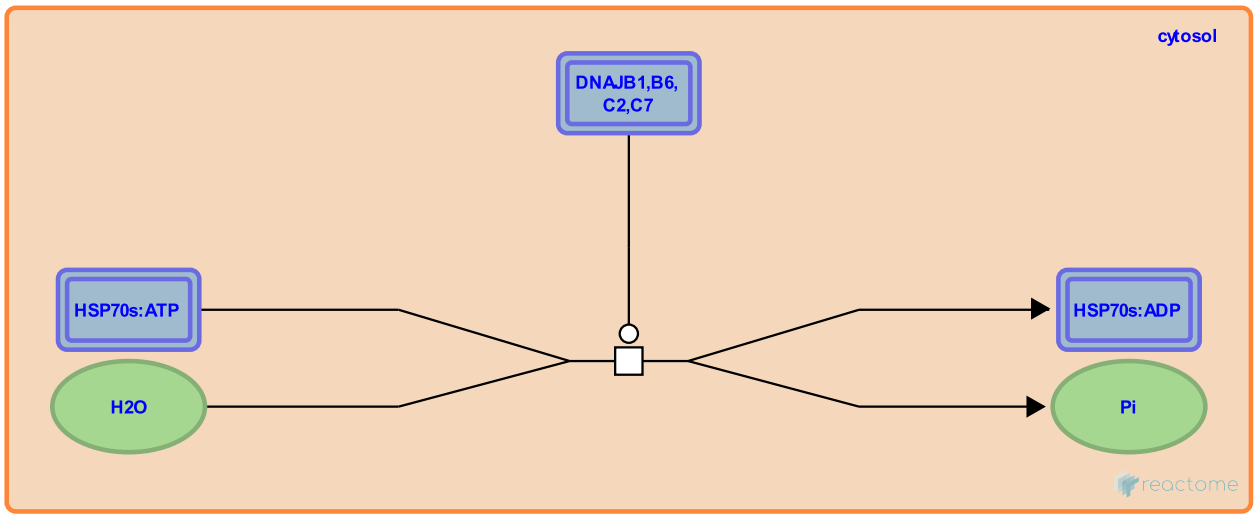
HSP40s activate intrinsic ATPase activity of HSP70s in the cytosol ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-5251959

Type: transition

Compartments: cytosol



Heat-shock 70kDa proteins (HSP70s) are a family of conserved, ubiquitously expressed heat-shock proteins which play important roles in protein folding and in protecting cells from stress. They possess three functional domains; an N-terminal ATPase domain, a substrate binding domain and a C-terminal domain. HSP70s are bound to either ATP or ADP. In the ATP-bound state, HSP70s do not interact with a substrate peptide as the C-terminal domain (which acts as a lid) is "open", allowing peptides to bind to the substrate binding domain but then be released very rapidily. However, a substrate peptide in the binding domain can stimulate the intrinsic ATPase activity of HSP70s, hydrolysing ATP to ADP. With ADP bound, the C-terminal domain of HSP70s closes around the peptide, effectively trapping the peptide.

Intrinsic ATPase activity proceeds relatively slowly but can be dramatically increased by binding of J-domain chaperones such as HSP40s. These are eukaryotic orthologues of the DnaJ cochaperones found in prokaryotes. The human HSP40s that are able to modulate intrinsic ATPase activity of HSP70s are DNAJB1, B6, C2 and C7 (Raabe & Manley 1991, Melville et al. 1999, Hanai & Mashima 2003, Izawa et al. 2000, Hundley et al. 2005, Brychzy et al. 2003). They are also able to co-localise to the nucleus with HSP70s upon heat-shock (Hattori et al. 1992).

Preceded by: HSP110s exchange ATP for ADP on HSP70s:ADP

Literature references

Hanai, R., Mashima, K. (2003). Characterization of two isoforms of a human DnaJ homologue, HSJ2. *Mol. Biol. Rep., 30*, 149-53. ↗

Hartl, FU., Rein, T., Obermann, WM., Young, JC., Winklhofer, KF., Brychzy, A. (2003). Cofactor Tpr2 combines two TPR domains and a J domain to regulate the Hsp70/Hsp90 chaperone system. *EMBO J., 22*, 3613-23. ↗

Tan, SL., Wambach, M., Song, J., Morimoto, RI., Melville, MW., Katze, MG. (1999). The cellular inhibitor of the PKR protein kinase, P58(IPK), is an influenza virus-activated co-chaperone that modulates heat shock protein 70 activity. *J. Biol. Chem., 274*, 3797-803. ↗

Hattori, H., Tanabe, K., Kobayashi, T., Ohtsuka, K., Kaneda, T., Ueda, M. et al. (1992). Intracellular localization and partial amino acid sequence of a stress-inducible 40-kDa protein in HeLa cells. *Cell Struct. Funct., 17*, 77-86. ↗

Raabe, T., Manley, JL. (1991). A human homologue of the Escherichia coli DnaJ heat-shock protein. *Nucleic Acids Res. , 19*, 6645. ↗

Editions

2014-02-05	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

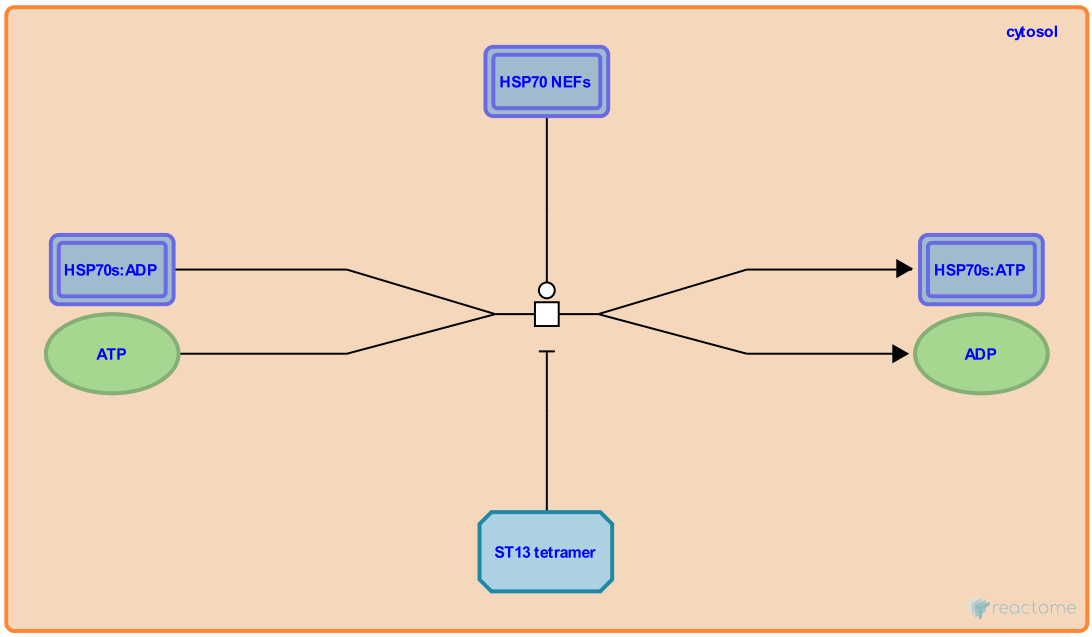
HSP110s exchange ATP for ADP on HSP70s:ADP ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-5252079

Type: transition

Compartments: cytosol



The substrate binding ability of heat-shock 70kDa proteins (HSP70s) is dependant on their bound state to either ATP or ADP. Release of a protein substrate is induced when HSP70s are bound to ATP and conversely, proteins substrates bind when HSP70s are bound to ADP. Intrinsic ATPase of HSP70s slowly hydrolyses ATP to ADP. This process can be speeded up by cochaperones such as HSP40s which stimulate ATPase activity. Nucleotide exchange factors (NEFs) regulate the lifespan of the HSP70:ADP:substrate complex by exchanging ADP for ATP, thus inducing the release of the substrate. Eukaryote NEFs include heat-shock protein 105kDa (HSPH1 aka HSP110) (Schuermann et al. 2008) and the BAG family molecular chaperone regulator (BAG) family (BAG1-5). BAGs inhibit the chaperone activity of HSP70s by promoting substrate release (Takayama et al. 1997, Takayama et al. 1999). HSC70-interacting protein (ST13 aka HIP) is a 48kDa tetrameric protein able to bind the ATPase domain of HSP70s and thought to stabilise the ADP state of HSP70s (Hohfeld et al. 1995, Prapapanich et al. 1996).

Followed by: HSP40s activate intrinsic ATPase activity of HSP70s in the cytosol

Literature references

Xie, Z., Matsuzawa, S., Freeman, BC., Reed, JC., Morimoto, RI., Bimston, DN. et al. (1997). BAG-1 modulates the chaperone activity of Hsp70/Hsc70. *EMBO J., 16*, 4887-96. ↗

Rimerman, RA., Chen, S., Smith, DF., Nair, SC., Prapapanich, V. (1996). Molecular cloning of human p48, a transient component of progesterone receptor complexes and an Hsp70-binding protein. *Mol. Endocrinol., 10*, 420-31. ↗

Xie, Z., Reed, JC., Takayama, S. (1999). An evolutionarily conserved family of Hsp70/Hsc70 molecular chaperone regulators. *J. Biol. Chem., 274*, 781-6. ↗

Hartl, FU., Minami, Y., Höhfeld, J. (1995). Hip, a novel cochaperone involved in the eukaryotic Hsc70/Hsp40 reaction cycle. *Cell, 83*, 589-98. ↗

Morano, KA., Lafer, EM., Demeler, B., Taylor, AB., Gimenez, LE., Jin, S. et al. (2008). Structure of the Hsp110:Hsc70 nucleotide exchange machine. *Mol. Cell, 31*, 232-43. ↗

Editions

2014-02-05	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

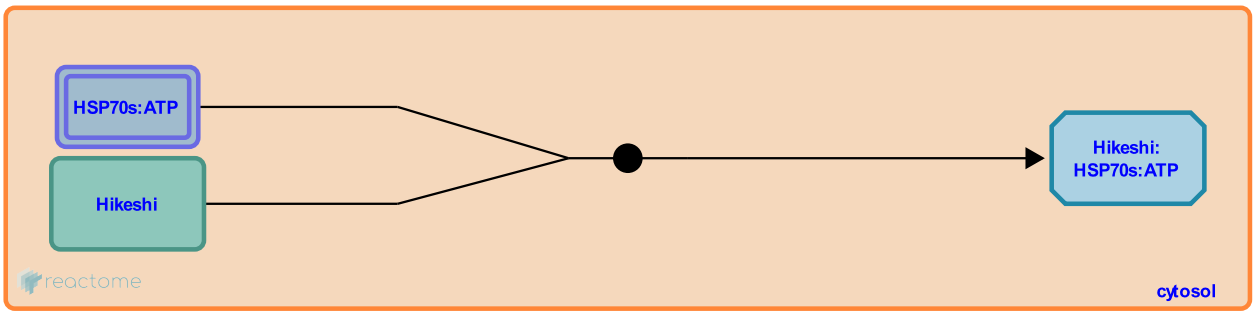
Hikeshi binds HSP70s:ATP ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-5251942

Type: binding

Compartments: cytosol



Protein Hikeshi (C11orf73) is a nuclear import carrier protein for heat-shock 70 proteins (HSP70s) in response to heat-shock stress. C11orf73 binds HSP70s in the cytosol, ready for nuclear import (Kose et al. 2012).

Literature references

Imamoto, N., Furuta, M., Kose, S. (2012). Hikeshi, a nuclear import carrier for Hsp70s, protects cells from heat shock-induced nuclear damage. *Cell, 149*, 578-89. ↗

Editions

2014-02-05	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

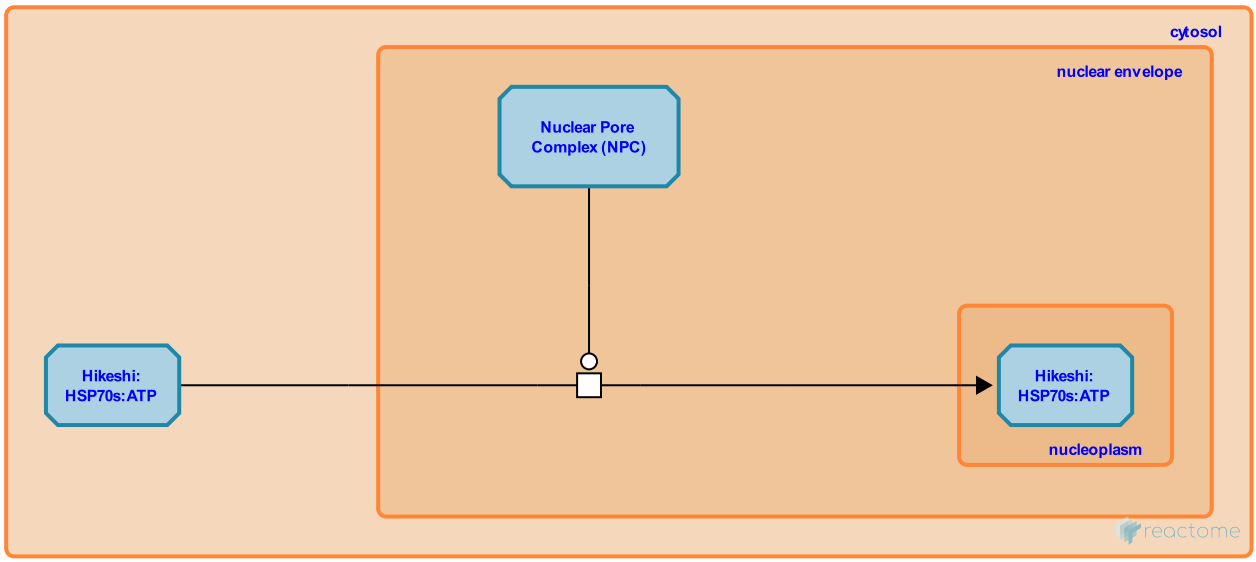
NPC transports Hikeshi:HSP70s:ATP from cytosol to nucleoplasm ↗

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-5252041

Type: transition

Compartments: nuclear envelope, nucleoplasm, cytosol



Protein Hikeshi (C11orf73) is a nuclear import carrier protein for heat-shock 70 proteins (HSP70s) in response to heat-shock stress. C11orf73-bound HSP70s bind to the nuclear pore complex (NPC) which transports the complex from the cytosol to the nucleoplasm where HSP70s can counteract heat shock-induced damage (Kose et al. 2012). NPC does not transport ADP-bound HSP70s.

Literature references

Imamoto, N., Furuta, M., Kose, S. (2012). Hikeshi, a nuclear import carrier for Hsp70s, protects cells from heat shock-induced nuclear damage. *Cell, 149*, 578-89. ↗

Editions

2014-02-05	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

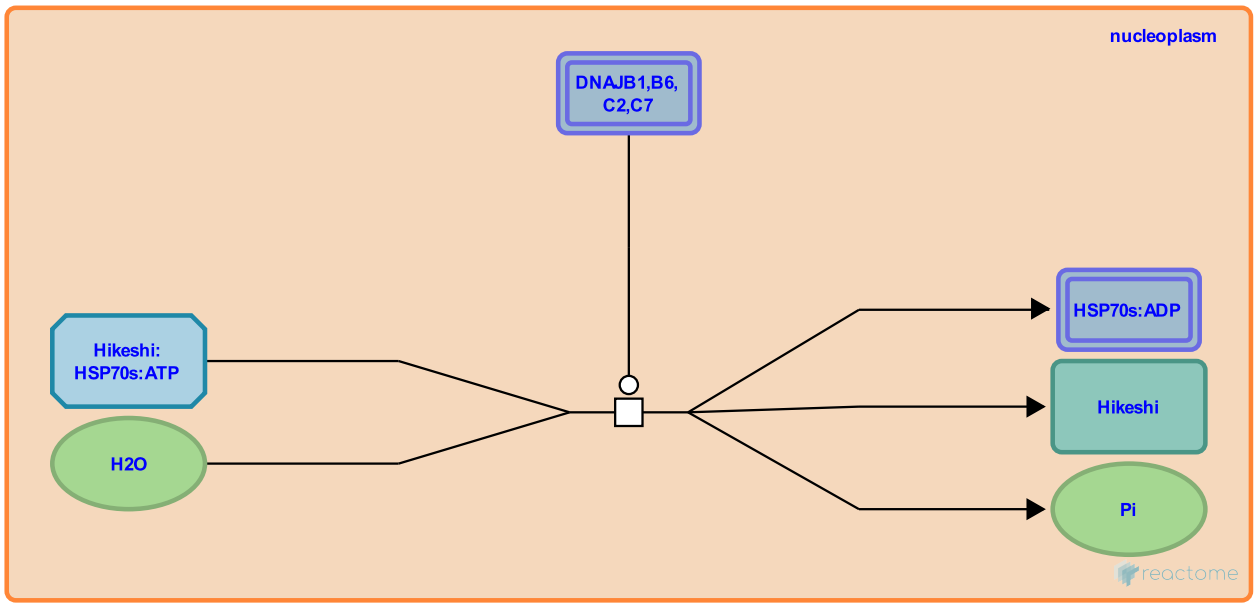
HSP40s activate intrinsic ATPase activity of HSP70s in the nucleoplasm

Location: Regulation of HSF1-mediated heat shock response

Stable identifier: R-HSA-5251955

Type: transition

Compartments: nucleoplasm



Protein Hikeshi (C11orf73) is a nuclear import carrier protein for heat-shock 70 proteins (HSP70s) in response to heat-shock stress. It is only able to bind HSP70s when they are bound to ATP. DnaJ homolog subfamily members (aka heat-shock 40 proteins, HSP40s) also translocate to the nucleus under heat-shock stress (Hattori et al. 1992) and can act as stimulators of intrinsic ATPase activity of HSP70s. The result is that Hikeshi dissociates from HSP70:ADP.

Literature references

Hattori, H., Tanabe, K., Kobayashi, T., Ohtsuka, K., Kaneda, T., Ueda, M. et al. (1992). Intracellular localization and partial amino acid sequence of a stress-inducible 40-kDa protein in HeLa cells. *Cell Struct. Funct., 17*, 77-86.

Editions

2014-02-05	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

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