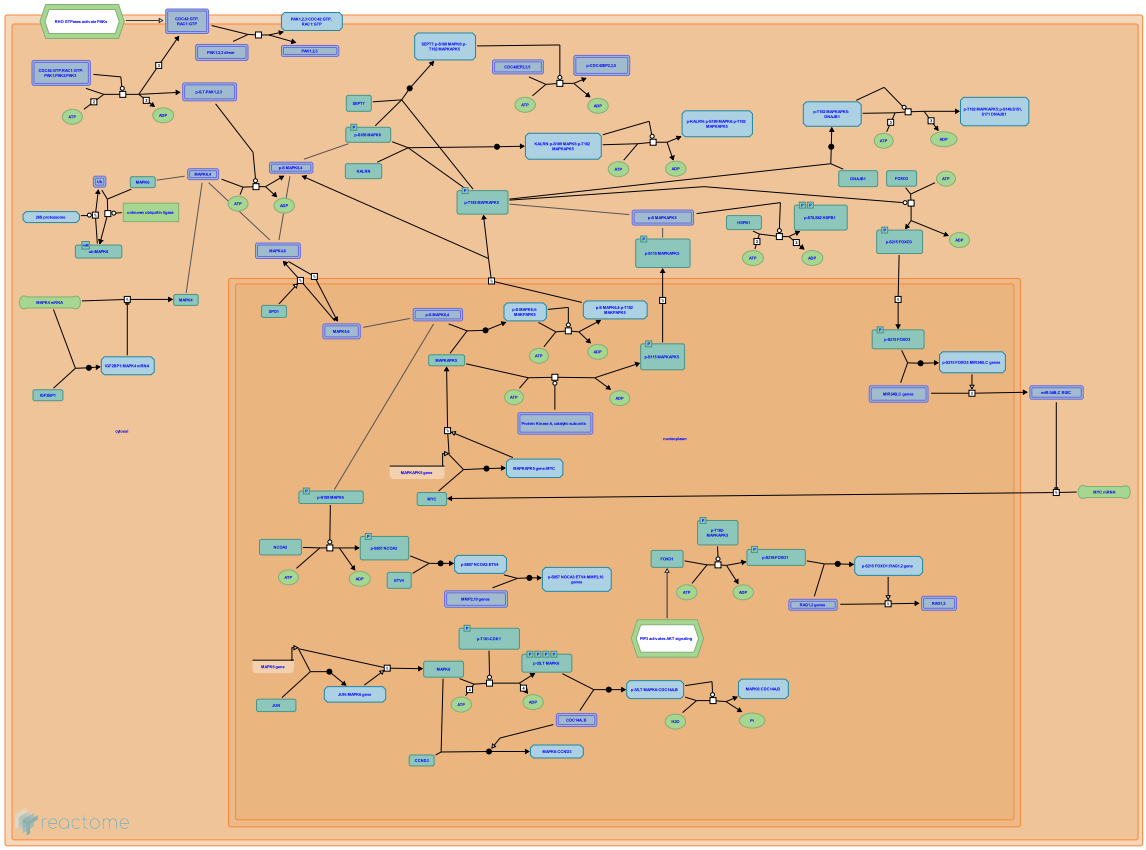
MAPK6/MAPK4 signaling



Bluestone, JA., Esensten, J., Garapati, P V., Mathien, S., Meloche, S., Moens, U., Orlic-Milacic, M., Rivero Crespo, F., Rothfels, K., Seternes, OM., Soulez, M.

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.

24/04/2024

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. ↗

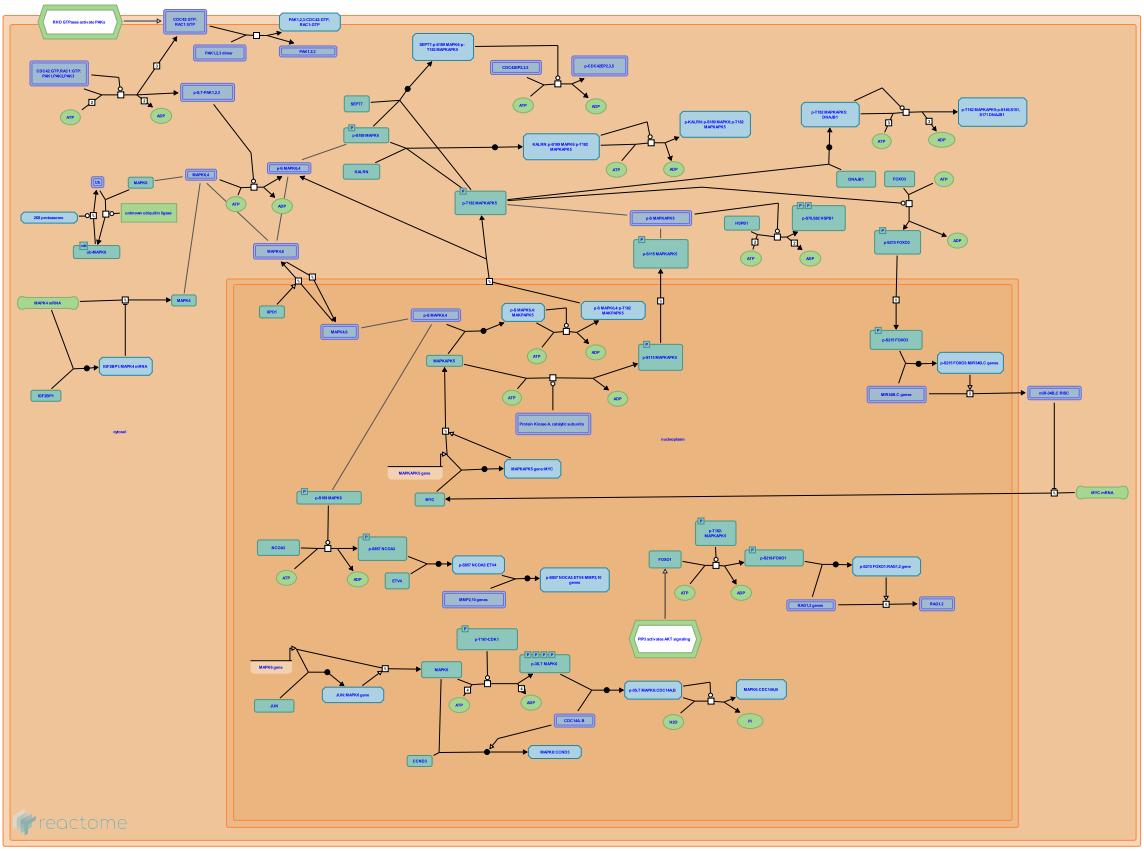
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

MAPK6/MAPK4 signaling ↗

Stable identifier: R-HSA-5687128



MAPK6 and MAPK4 (also known as ERK3 and ERK4) are vertebrate-specific atypical MAP kinases. Atypical MAPK are less well characterized than their conventional counterparts, and are generally classified as such based on their lack of activation by MAPKK family members. Unlike the conventional MAPK proteins, which contain a Thr-X-Tyr motif in the activation loop, MAPK6 and 4 have a single Ser-Glu-Gly phospho-acceptor motif (reviewed in Coulombe and Meloche, 2007; Cargnello et al, 2011). MAPK6 is also distinct in being an unstable kinase, whose turnover is mediated by ubiquitin-dependent degradation (Coulombe et al, 2003; Coulombe et al, 2004). The biological functions and pathways governing MAPK6 and 4 are not well established. MAPK6 and 4 are phosphorylated downstream of class I p21 activated kinases (PAKs) in a RAC- or CDC42-dependent manner (Deleris et al, 2008; Perander et al, 2008; Deleris et al, 2011; De La Mota-Peynado et al, 2011). One of the only well established substrates of MAPK6 and 4 is MAPKAPK5, which contributes to cell motility by promoting the HSBP1-dependent rearrangement of F-actin (Gerits et al, 2007; Kostenko et al, 2009a; reviewed in Kostenko et al, 2011b). The atypical MAPKs also contribute to cell motility and invasiveness through the NCOA3:ETV4-dependent regulation of MMP gene expression (Long et al, 2012; Yan et al, 2008; Qin et al, 2008). Both of these pathways may be misregulated in human cancers (reviewed in Myant and Sansom, 2011; Kostenko et al, 2012)

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Erdem, H., Tsai, SY., Yan, J., Li, R., Tsai, MJ., Ittmann, M. et al. (2008). Steroid receptor coactivator-3/AIB1 promotes cell migration and invasiveness through focal adhesion turnover and matrix metalloproteinase expression. *Cancer Res., 68*, 5460-8. ↗

Meloche, S., Coulombe, P. (2007). Atypical mitogen-activated protein kinases: structure, regulation and functions. *Biochim. Biophys. Acta, 1773*, 1376-87. ↗

Déléris, P., Rousseau, J., Meloche, S., Rodier, G., Coulombe, P., Tanguay, PL. (2008). Activation loop phosphorylation of the atypical MAP kinases ERK3 and ERK4 is required for binding, activation and cytoplasmic relocalization of MK5. *J. Cell. Physiol., 217*, 778-88. ↗

Myant, K., Sansom, OJ. (2011). More, more, more: downregulation of a MK5-FoxO3a-mir34b/c pathway further increases c-Myc levels in colorectal cancer. *Mol. Cell, 41*, 369-70. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
2015-05-05	Reviewed	Seternes, OM.
2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

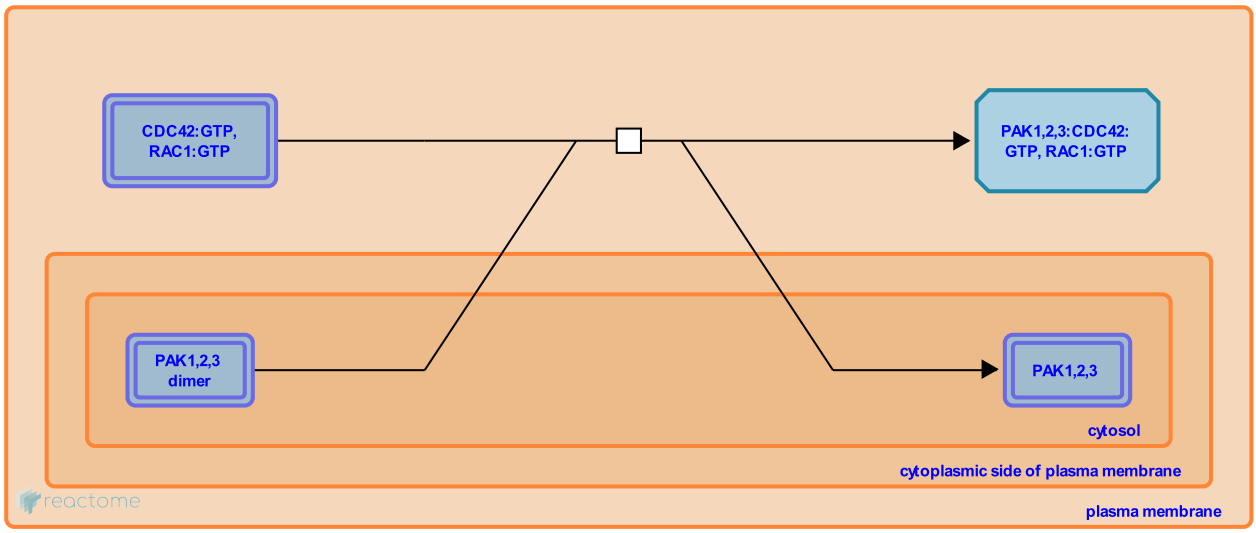
Activation of PAKs by RAC1 and CDC42 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-389788

Type: transition

Compartments: plasma membrane, cytosol



Inactive p21-associated kinases (PAKs), PAK1, PAK2 and PAK3, form homodimers that are autoinhibited through in trans interaction between the inhibitory N-terminus of one PAK molecule and the catalytic domain of the other PAK molecule. All PAK isoforms are direct effectors of RAC1 and CDC42 GTPases. RAC1 and CDC42 bind to a highly conserved motif in the amino terminus of PAK known as p21-binding domain (PBD) or Cdc42/Rac interactive binding (CRIB) domain. This binding induces a conformational change that disrupts PAK homodimers and relieves autoinhibition of the catalytic carboxyl terminal domain, thereby inducing autophosphorylation at several sites and enabling the phosphorylation of exogenous substrates (Manser et al. 1994, Manser et al. 1995, Zhang et al. 1998, Lei et al. 2000, Parrini et al. 2002; reviewed by Daniels and Bokoch 1999, Szczepanowska 2009).

Literature references

Parrini, MC., Lei, M., Mayer, BJ., Harrison, SC. (2002). Pak1 kinase homodimers are autoinhibited in trans and dissociated upon activation by Cdc42 and Rac1. *Mol Cell, 9*, 73-83. ↗

Manser, E., Leung, T., Lim, L., Zhao, ZS., Salihuddin, H. (1994). A brain serine/threonine protein kinase activated by Cdc42 and Rac1. *Nature, 367*, 40-6. ↗

Szczepanowska, J. (2009). Involvement of Rac/Cdc42/PAK pathway in cytoskeletal rearrangements. *Acta Biochim Pol, 56*, 225-34. ↗

Bokoch, GM., Daniels, RH. (1999). p21-activated protein kinase: a crucial component of morphological signaling?. *Trends Biochem Sci, 24*, 350-5. ↗

Zhang, B., Chernoff, J., Zheng, Y. (1998). Interaction of Rac1 with GTPase-activating proteins and putative effectors. A comparison with Cdc42 and RhoA. *J. Biol. Chem., 273*, 8776-82. ↗

Editions

2008-07-16	Authored	Garapati, P V.
2008-12-16	Edited	Garapati, P V.
2009-06-01	Reviewed	Bluestone, JA., Esensten, J.
2014-12-26	Reviewed	Rivero Crespo, F.

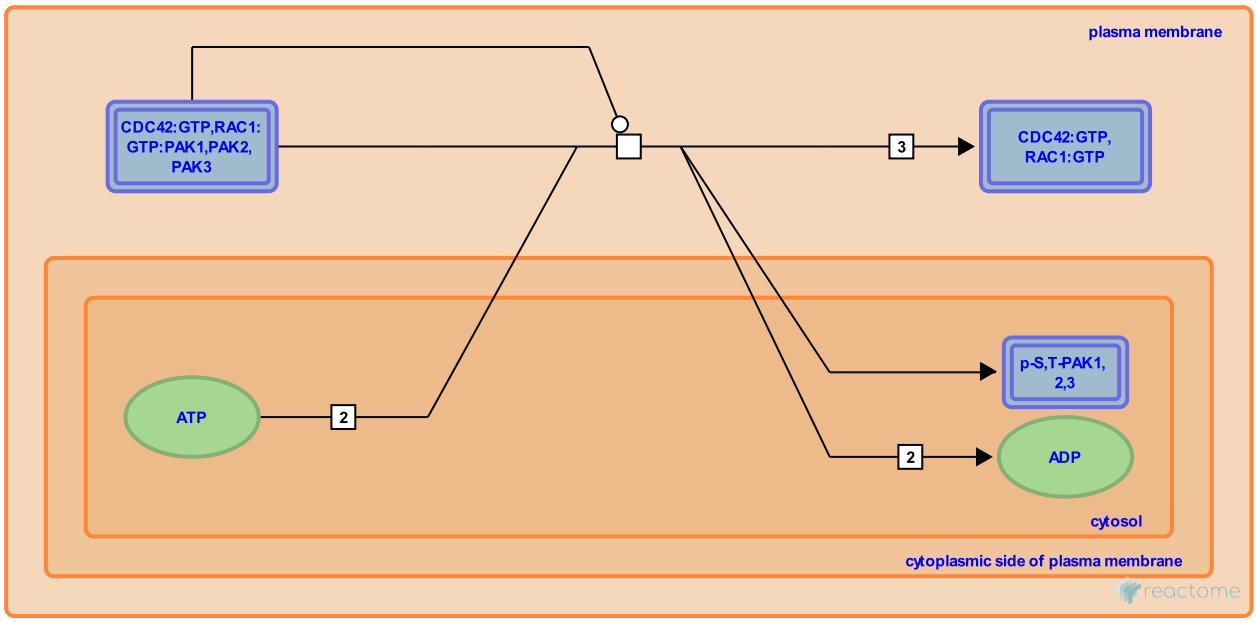
Autophosphorylation of PAK1,2,3 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5627775

Type: transition

Compartments: plasma membrane, cytosol



Binding of PAK1, PAK2 or PAK3 to GTP-bound RAC1 or CDC42 disrupts PAK homodimers and allows PAK autophosphorylation. Autophosphorylation of a conserved threonine residue in the catalytic domain of PAKs (T423 in PAK1, T402 in PAK2 and T436 in PAK3) is necessary for the kinase activity of PAK1, PAK2 and PAK3. Autophosphorylation of PAK1 serine residue S144, PAK2 serine residue S141, and PAK3 serine residue S154 disrupts association of PAKs with RAC1 or CDC42 GTPases and enhances kinase activity (Lei et al. 2000, Chong et al. 2001, Parrini et al. 2002, Jung and Traugh 2005, Wang et al. 2011).

Followed by: PAK1,2,3 phosphorylates MAPK6,4

Literature references

Parrini, MC., Lei, M., Mayer, BJ., Harrison, SC. (2002). Pak1 kinase homodimers are autoinhibited in trans and dissociated upon activation by Cdc42 and Rac1. *Mol Cell, 9*, 73-83. ↗

Wu, JW., Wang, J., Wang, ZX. (2011). Mechanistic studies of the autoactivation of PAK2: a two-step model of cis initiation followed by trans amplification. *J. Biol. Chem., 286*, 2689-95. ↗

Traugh, JA., Jung, JH. (2005). Regulation of the interaction of Pak2 with Cdc42 via autophosphorylation of serine 141. *J Biol Chem, 280*, 40025-31. ↗

Manser, E., Lim, L., Chong, C., Tan, L. (2001). The mechanism of PAK activation. Autophosphorylation events in both regulatory and kinase domains control activity. *J Biol Chem, 276*, 17347-53. ↗

Meng, W., Mayer, BJ., Eck, MJ., Lu, W., Parrini, MC., Lei, M. et al. (2000). Structure of PAK1 in an autoinhibited conformation reveals a multistage activation switch. *Cell, 102*, 387-97. ↗

Editions

2014-10-24	Authored	Orlic-Milacic, M.
2014-12-26	Authored	Rivero Crespo, F.
2015-02-02	Edited	Orlic-Milacic, M.
2017-03-15	Edited	Orlic-Milacic, M.

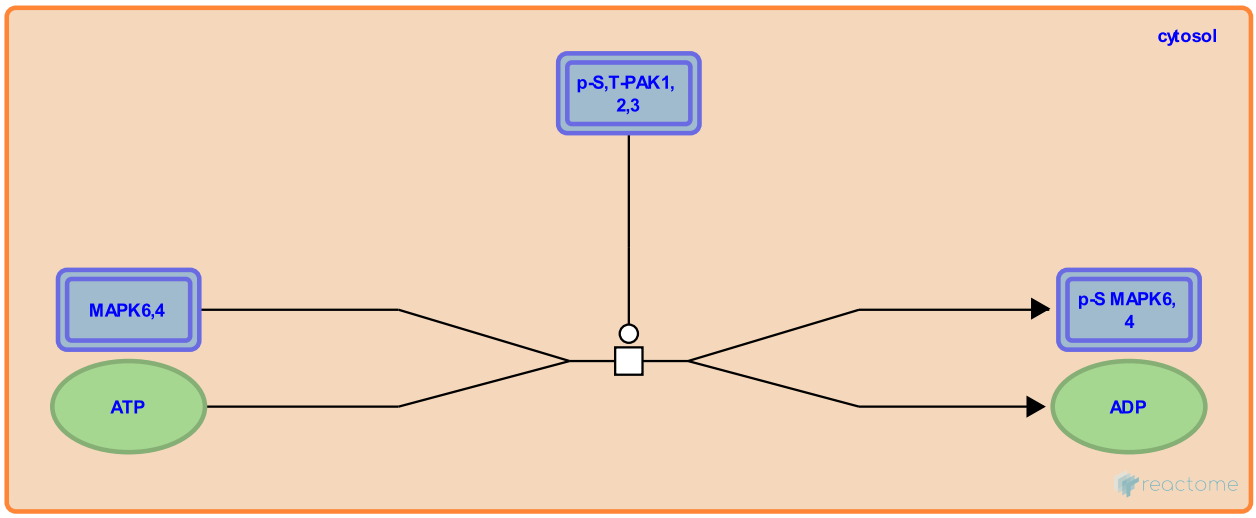
PAK1,2,3 phosphorylates MAPK6,4 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687086

Type: transition

Compartments: cytosol



The atypical MAPKs MAPK6 (also known as ERK3) and MAPK4 (also known as ERK4) lack the conserved activation loop T-X-Y motif of the conventional MAPKs, and are thus not substrates for the dual-specificity MAPK kinases (reviewed in Coulombe and Meloche, 2007; Cargnello and Roux, 2011). The corresponding loop of MAPK6 and 4 instead contain a S-E-G motif that is phosphorylated at serine 189 and serine 186, respectively, by class I p21 activated kinases (PAKs) in a RAC- or CDC42-dependent manner (Deleris et al, 2008; Perander et al, 2008; Deleris et al, 2011; De La Mota-Peynado et al, 2011). Phosphorylation of the atypical MAPKs is not responsive to any identified extracellular stimulus, but rather occurs constitutively (Deleris et al, 2008).

Preceded by: Autophosphorylation of PAK1,2,3

Literature references

Meloche, S., Coulombe, P. (2007). Atypical mitogen-activated protein kinases: structure, regulation and functions. *Biochim. Biophys. Acta, 1773*, 1376-87. ↗

De la Mota-Peynado, A., Beeser, A., Chernoff, J. (2011). Identification of the atypical MAPK Erk3 as a novel substrate for p21-activated kinase (Pak) activity. *J. Biol. Chem., 286*, 13603-11. ↗

Déléris, P., Rousseau, J., Meloche, S., Rodier, G., Coulombe, P., Tanguay, PL. (2008). Activation loop phosphorylation of the atypical MAP kinases ERK3 and ERK4 is required for binding, activation and cytoplasmic relocalization of MK5. *J. Cell. Physiol., 217*, 778-88. ↗

Johansen, B., Aberg, E., Keyse, SM., Perander, M., Dreyer, B., Guldvik, IJ. et al. (2008). The Ser(186) phospho-acceptor site within ERK4 is essential for its ability to interact with and activate PRAK/MK5. *Biochem. J., 411*, 613-22. ↗

Déléris, P., Meloche, S., Tanguay, PL., Borden, KL., Trost, M., Thibault, P. et al. (2011). Activation loop phosphorylation of ERK3/ERK4 by group I p21-activated kinases (PAKs) defines a novel PAK-ERK3/4-MAPK-activated protein kinase 5 signaling pathway. *J. Biol. Chem., 286*, 6470-8. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
2015-05-05	Reviewed	Seternes, OM.
2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

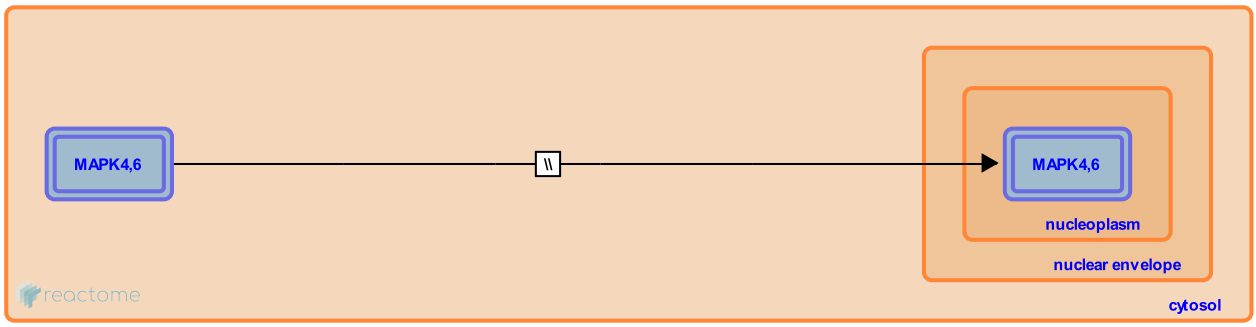
MAPK4,6 translocate to nucleus ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687107

Type: omitted

Compartments: cytosol



Despite differences in their overall cellular distribution (MAPK6 is found in both the nucleus and the cytosol, while MAPK4 is predominantly found in the cytosol), both MAPK4 and 6 shuttle between the cytosol and the nucleus. Nuclear import of both proteins occurs through an active temperature sensitive pathway, while nuclear export depends on XPO1 (Aberg et al, 2006; Julien et al, 2003).

Followed by: p-S MAPK6 phosphorylates NCOA3, p-S MAPK6,4 binds MAPKAPK5

Literature references

Meloche, S., Julien, C., Johansen, B., Aberg, E., Keyse, SM., Perander, M. et al. (2006). Regulation of MAPK-activated protein kinase 5 activity and subcellular localization by the atypical MAPK ERK4/MAPK4. *J. Biol. Chem., 281*, 35499-510. ↗

Meloche, S., Julien, C., Coulombe, P. (2003). Nuclear export of ERK3 by a CRM1-dependent mechanism regulates its inhibitory action on cell cycle progression. *J. Biol. Chem., 278*, 42615-24. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
2015-05-05	Reviewed	Seternes, OM.
2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

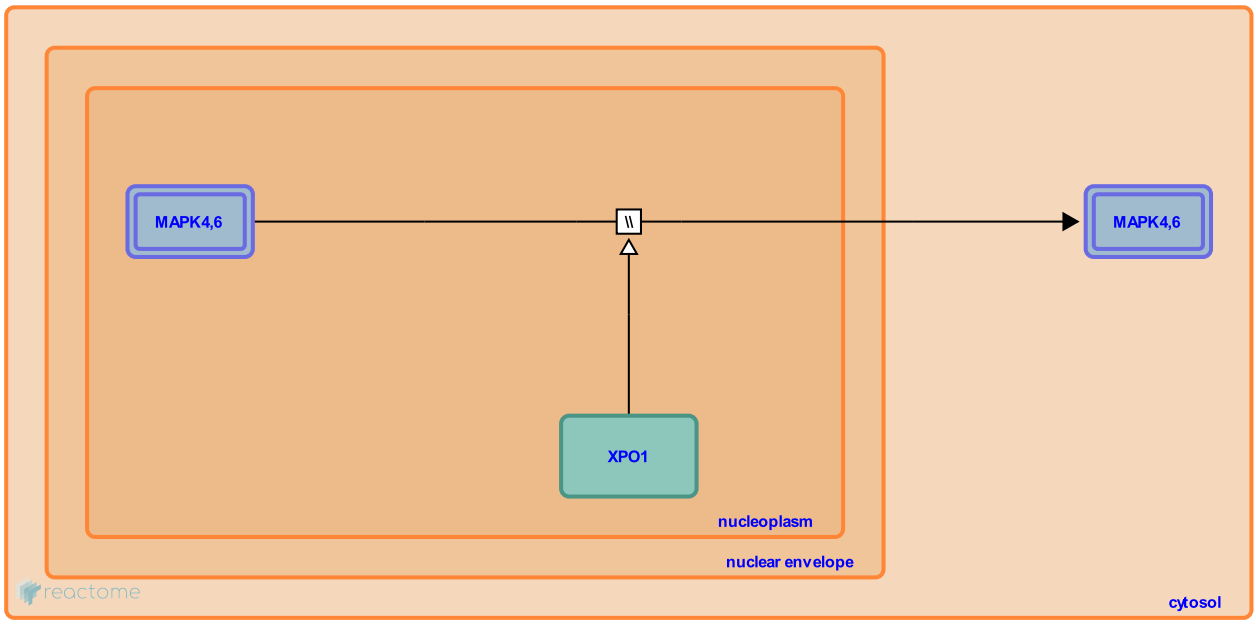
MAPK4,6 translocate to the cytoplasm ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687109

Type: omitted

Compartments: nucleoplasm



Despite differences in their overall cellular distribution (MAPK6 is found in both the nucleus and the cytosol, while MAPK4 is predominantly found in the cytosol), both MAPK4 and 6 shuttle between the cytosol and the nucleus. Nuclear import of both proteins occurs through an active temperature sensitive pathway, while nuclear export depends on XPO1 (Aberg et al, 2006; Julien et al, 2003).

Literature references

Meloche, S., Julien, C., Johansen, B., Aberg, E., Keyse, SM., Perander, M. et al. (2006). Regulation of MAPK-activated protein kinase 5 activity and subcellular localization by the atypical MAPK ERK4/MAPK4. *J. Biol. Chem., 281*, 35499-510. ↗

Meloche, S., Julien, C., Coulombe, P. (2003). Nuclear export of ERK3 by a CRM1-dependent mechanism regulates its inhibitory action on cell cycle progression. *J. Biol. Chem., 278*, 42615-24. ↗

Editions

2015-03-30	Authored	Rothfels, K.
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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

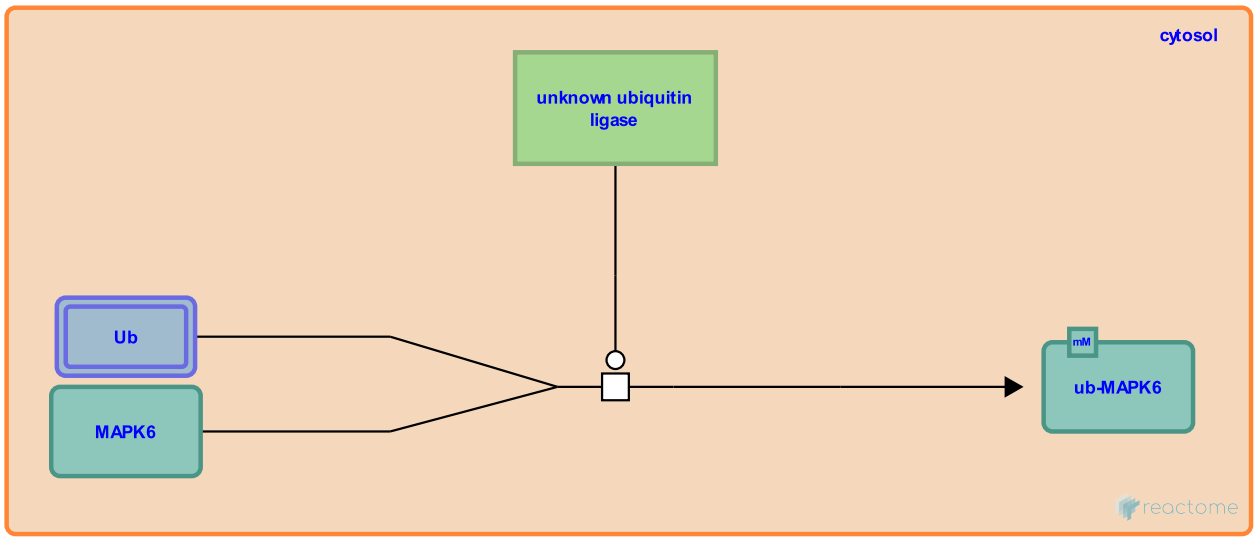
MAPK6 is ubiquitinated at the N-terminal ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687081

Type: transition

Compartments: cytosol



MAPK6 is an unstable protein that is constitutively degraded by the ubiquitin-proteasome system. Degradation is promoted by two destabilization regions in the N-terminal region of MAPK6 which are required for the conjugation of ubiquitin to the free amino-terminal by an unknown ligase (Coulombe et al, 2003; Coulombe et al, 2004). Although in this reaction ubiquitination is depicted as occuring in the cytosol, it may also occur in the nucleus.

Followed by: MAPK6 is degraded by the 26S proteasome

Literature references

Meloche, S., Rodier, G., Coulombe, P., Bonneil, E., Thibault, P. (2004). N-Terminal ubiquitination of extracellular signal-regulated kinase 3 and p21 directs their degradation by the proteasome. *Mol. Cell. Biol., 24*, 6140-50. ↗

Meloche, S., Rodier, G., Coulombe, P., Pelletier, S., Pellerin, J. (2003). Rapid turnover of extracellular signal-regulated kinase 3 by the ubiquitin-proteasome pathway defines a novel paradigm of mitogen-activated protein kinase regulation during cellular differentiation. *Mol. Cell. Biol., 23*, 4542-58. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
2015-05-05	Reviewed	Seternes, OM.
2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

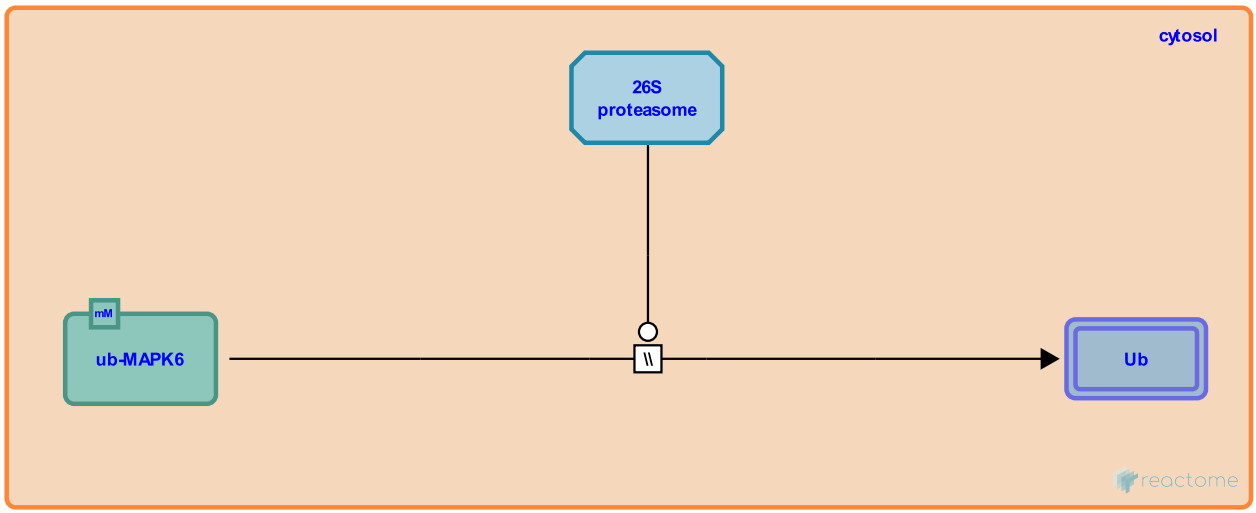
MAPK6 is degraded by the 26S proteasome ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687112

Type: omitted

Compartments: cytosol



MAPK6 is a short-lived protein with a half-life of 30 minutes in proliferating cells. Turnover is promoted by the conjugation of ubiquitin to the free amino terminal by an unknown ligase and subsequent degradation by the 26 S proteasome (Coulombe et al, 2003; Coulombe et al, 2004). Ubiquitination and degradation of MAPK6 may also occur in the nucleus as well as the cytosol.

Preceded by: MAPK6 is ubiquitinated at the N-terminal

Literature references

Meloche, S., Rodier, G., Coulombe, P., Bonneil, E., Thibault, P. (2004). N-Terminal ubiquitination of extracellular signal-regulated kinase 3 and p21 directs their degradation by the proteasome. *Mol. Cell. Biol., 24*, 6140-50. ↗

Meloche, S., Rodier, G., Coulombe, P., Pelletier, S., Pellerin, J. (2003). Rapid turnover of extracellular signal-regulated kinase 3 by the ubiquitin-proteasome pathway defines a novel paradigm of mitogen-activated protein kinase regulation during cellular differentiation. *Mol. Cell. Biol., 23*, 4542-58. ↗

Editions

2015-04-06	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
2015-05-05	Reviewed	Seternes, OM.
2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

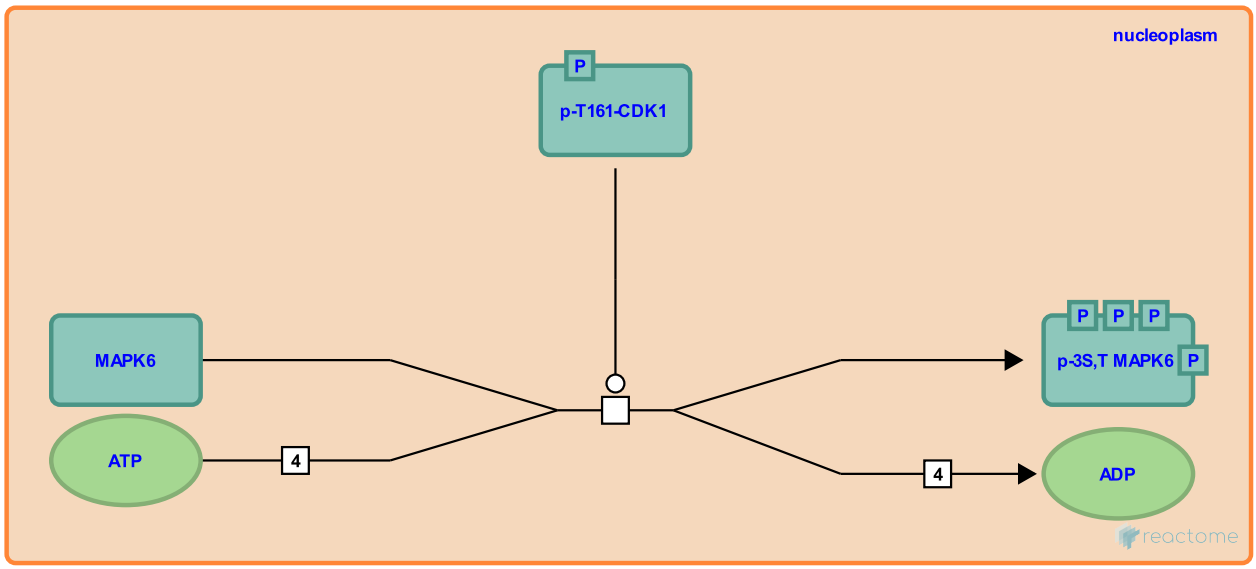
CDK1 phosphorylates MAPK6 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692755

Type: transition

Compartments: nucleoplasm



MAPK6 is hyperphosphorylated by CDK1 at multiple sites in the C-terminal extension, and this phosphorylation is associated with the stabilization of MAPK6 protein in mitosis. Residues S684, S688, T698 and S705 have been identified as in vitro targets of CDK1, and phosphorylation of T698 has also been demonstrated in vivo (Tanguay et al, 2010). The role of hyperphosphorylated MAPK6 during mitosis has not been established, and although the CDK1-dependent phosphorylation of MAPK6 is depicted as occuring in the nucleus, the site of action has also not been determined. CDK1-dependent hyperphosphorylation of the C-terminal tail is reversed by the phosphatases CDC14A and B (Tanguay et al, 2010; Hansen et al, 2008).

Literature references

Meloche, S., Rodier, G., Tanguay, PL. (2010). C-terminal domain phosphorylation of ERK3 controlled by Cdk1 and Cdc14 regulates its stability in mitosis. *Biochem. J., 428*, 103-11. ↗

Bartek, J., Hansen, CA., Jensen, S. (2008). A functional link between the human cell cycle-regulatory phosphatase Cdc14A and the atypical mitogen-activated kinase Erk3. *Cell Cycle, 7*, 325-34. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
2015-05-12	Authored, Reviewed	Meloche, S., Soulez, M.
2015-05-13	Edited	Rothfels, K.

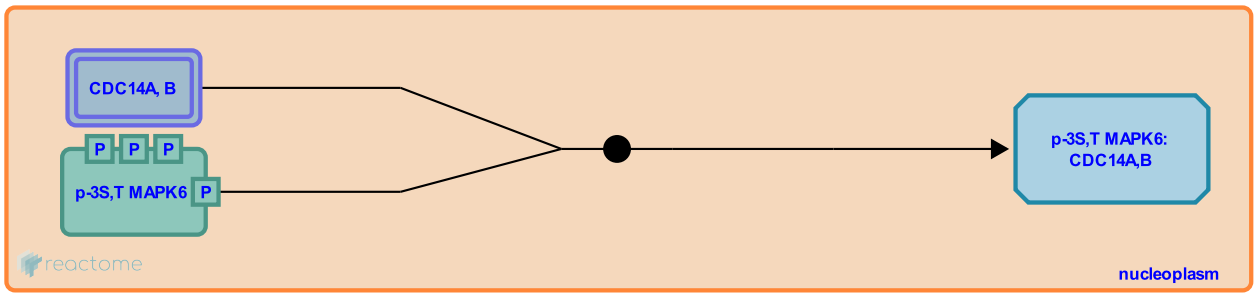
CDC14A,B bind MAPK6 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692749

Type: binding

Compartments: nucleoplasm



The phosphatases CDC14A and CDC14B bind directly to MAPK6 as assessed by yeast two hybrid and by co-immunoprecipitation (Tanguay et al, 2010; Hansen et al, 2008). CDC14 phosphatases are able to reverse the CDK1-dependent phosphorylation of MAPK6 in vitro, and overexpression of WT but not catalytically inactive forms of CDC14A or B in vivo leads to dephosphorylation of T698 (Hansen et al, 2008; Tanguay et al, 2010). These results suggest that CDC14 phosphatases reverse the CDK1-dependent phosphorylation of MAPK6 during mitosis. These reactions are depicted as occuring in the nucleoplasm, but the site of action has not been determined, and CDC14 and MAPK6 colocalize throughout the cell (Hansen et al, 2008).

Literature references

Meloche, S., Rodier, G., Tanguay, PL. (2010). C-terminal domain phosphorylation of ERK3 controlled by Cdk1 and Cdc14 regulates its stability in mitosis. *Biochem. J., 428*, 103-11. ↗

Bartek, J., Hansen, CA., Jensen, S. (2008). A functional link between the human cell cycle-regulatory phosphatase Cdc14A and the atypical mitogen-activated kinase Erk3. *Cell Cycle, 7*, 325-34. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
2015-05-12	Authored, Reviewed	Meloche, S., Soulez, M.
2015-05-13	Edited	Rothfels, K.

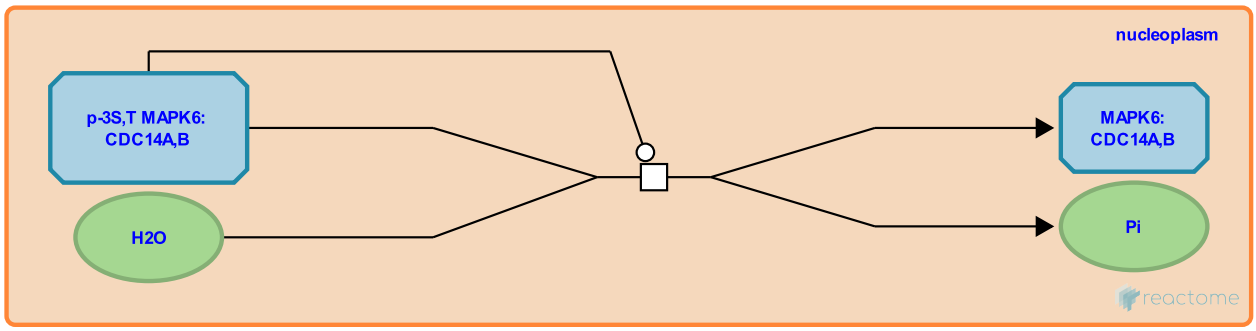
CDC14A,B dephosphorylate p-3S,T MAPK6 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692754

Type: transition

Compartments: nucleoplasm



CDC14A and B bind to MAPK6 and antagonize the CDK1-dependent phosphorylation of the C-terminal extension during mitosis (Tanguay et al, 2010; Hansen et al, 2008).

Literature references

Meloche, S., Rodier, G., Tanguay, PL. (2010). C-terminal domain phosphorylation of ERK3 controlled by Cdk1 and Cdc14 regulates its stability in mitosis. *Biochem. J., 428*, 103-11. ↗

Bartek, J., Hansen, CA., Jensen, S. (2008). A functional link between the human cell cycle-regulatory phosphatase Cdc14A and the atypical mitogen-activated kinase Erk3. *Cell Cycle, 7*, 325-34. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
2015-05-12	Authored, Reviewed	Meloche, S., Soulez, M.
2015-05-13	Edited	Rothfels, K.

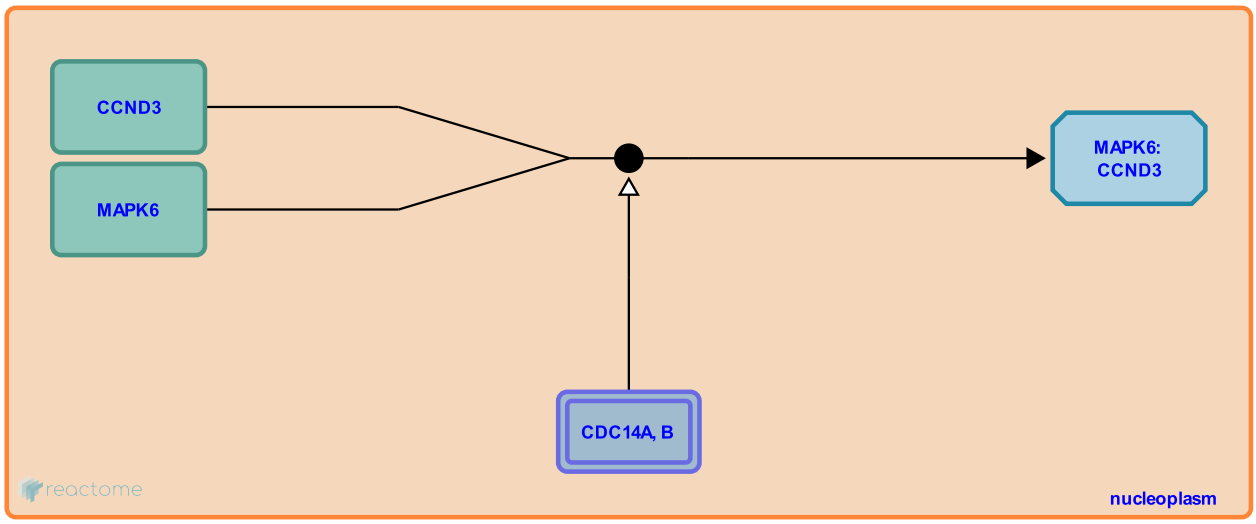
MAPK6 binds CCND3 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692764

Type: binding

Compartments: nucleoplasm



MAPK6 interacts with Cyclin D3 (CCND3) through its C-terminal extension, and this interaction is stabilized by overexpression of CDC14 phosphatase (Sun et al, 2006; Hansen et al, 2008). Although the physiological relevance of the interaction between MAPK6 and CCND3 is not known, both proteins regulate cell cycle entry and MAPK6 is stabilized during differentiation and upon inhibition of proliferation (Coulombe et al, 2003; Bartkova et al, 1998; Julien et al, 2003).

Literature references

Strauss, M., Lukas, J., Bartek, J., Bartkova, J. (1998). Cyclin D3: requirement for G1/S transition and high abundance in quiescent tissues suggest a dual role in proliferation and differentiation. *Oncogene, 17*, 1027-37. ↗

Bartek, J., Hansen, CA., Jensen, S. (2008). A functional link between the human cell cycle-regulatory phosphatase Cdc14A and the atypical mitogen-activated kinase Erk3. *Cell Cycle, 7*, 325-34. ↗

Meloche, S., Julien, C., Coulombe, P. (2003). Nuclear export of ERK3 by a CRM1-dependent mechanism regulates its inhibitory action on cell cycle progression. *J. Biol. Chem., 278*, 42615-24. ↗

Meloche, S., Rodier, G., Coulombe, P., Pelletier, S., Pellerin, J. (2003). Rapid turnover of extracellular signal-regulated kinase 3 by the ubiquitin-proteasome pathway defines a novel paradigm of mitogen-activated protein kinase regulation during cellular differentiation. *Mol. Cell. Biol., 23*, 4542-58. ↗

Wei, Y., Chen, X., Jiang, J., Xie, J., Gu, J., Wang, H. et al. (2006). Identification of extracellular signal-regulated kinase 3 as a new interaction partner of cyclin D3. *Biochem. Biophys. Res. Commun., 340*, 209-14. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
2015-05-12	Authored, Reviewed	Meloche, S., Soulez, M.
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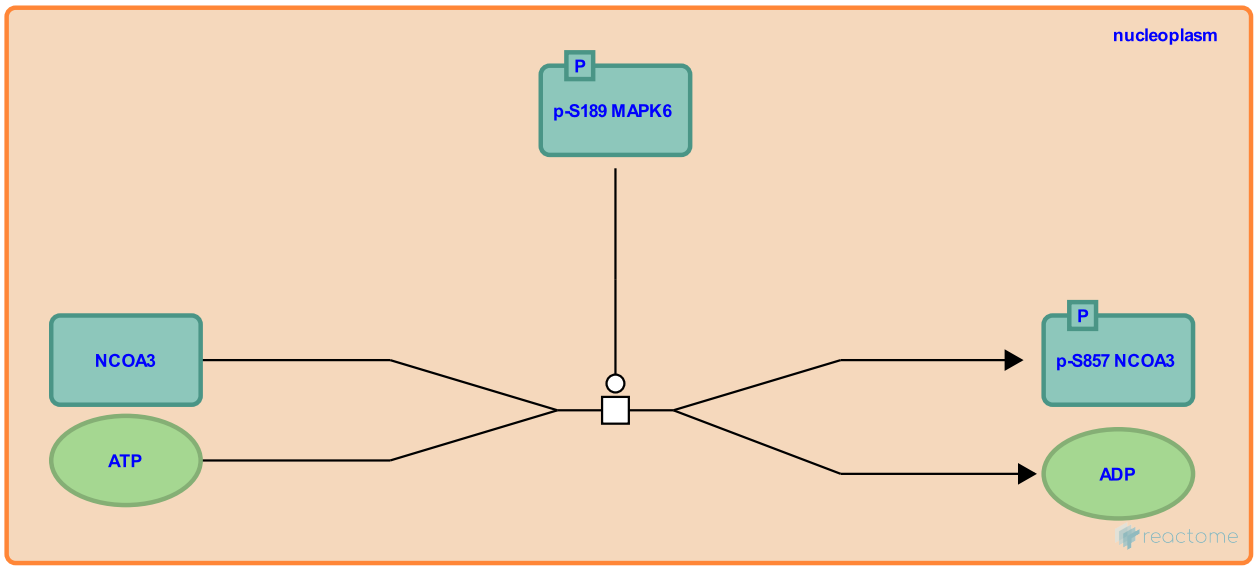
p-S MAPK6 phosphorylates NCOA3 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687090

Type: transition

Compartments: nucleoplasm



MAPK6 is proposed to phosphorylate NCOA3 at serine 857. This phosphorylation is required for NCOA3 to interact with the transcription factor ETV4 (also known as PEA3). Together, ETV4 and NCOA3 bind to the promoters and regulate the expression of metalloprotease genes such as MMP2 and MMP10 and in this way contribute to cell motility and invasiveness in lung cancer (Long et al, 2012; Qin et al, 2008; Yan et al, 2008; Li et al, 2008; reviewed in Kostenko et al, 2012).

Preceded by: MAPK4,6 translocate to nucleus

Followed by: p-S857 NCOA3 binds ETV4

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Erdem, H., Tsai, SY., Yan, J., Li, R., Tsai, MJ., Ittmann, M. et al. (2008). Steroid receptor coactivator-3/AIB1 promotes cell migration and invasiveness through focal adhesion turnover and matrix metalloproteinase expression. *Cancer Res., 68*, 5460-8. ↗

O'Malley, BW., Foulds, CE., Tsai, SY., Liu, J., Long, W., Tsai, MJ. et al. (2012). ERK3 signals through SRC-3 coactivator to promote human lung cancer cell invasion. *J. Clin. Invest., 122*, 1869-80. ↗

Louie, MC., Zou, JX., Li, LB., Chen, HW. (2008). Proto-oncogene ACTR/AIB1 promotes cancer cell invasion by up-regulating specific matrix metalloproteinase expression. *Cancer Lett., 261*, 64-73. ↗

O'Malley, BW., Redmond, A., Yuan, Y., Chen, H., Qin, L., Xu, J. et al. (2008). The AIB1 oncogene promotes breast cancer metastasis by activation of PEA3-mediated matrix metalloproteinase 2 (MMP2) and MMP9 expression. *Mol. Cell. Biol., 28*, 5937-50. ↗

Editions

2015-04-03	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
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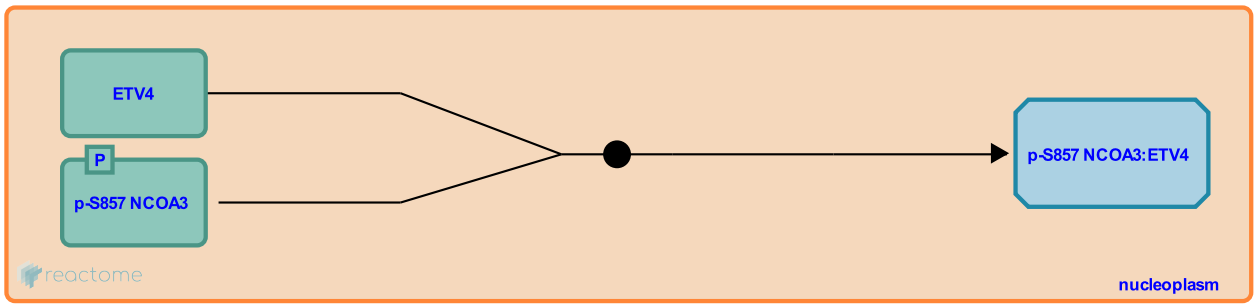
p-S857 NCOA3 binds ETV4 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687097

Type: binding

Compartments: nucleoplasm



NCOA3 interacts with ETV4 (also known as PEA3) in a manner that depends on S857 phosphorylation (Long et al, 2012). ETV4 and NCOA3 coactivate expression of a number of MMP genes, which play roles in cell motility and invasiveness in a subset of lung carcinomas (Long et al, 2012; Qin et al, 2008; Yan et al, 2008).

Preceded by: p-S MAPK6 phosphorylates NCOA3

Followed by: p-S857 NCOA3:ETV4 bind MMP2 and MMP10 promoter

Literature references

Erdem, H., Tsai, SY., Yan, J., Li, R., Tsai, MJ., Ittmann, M. et al. (2008). Steroid receptor coactivator-3/AIB1 promotes cell migration and invasiveness through focal adhesion turnover and matrix metalloproteinase expression. *Cancer Res., 68*, 5460-8. ↗

O'Malley, BW., Foulds, CE., Tsai, SY., Liu, J., Long, W., Tsai, MJ. et al. (2012). ERK3 signals through SRC-3 coactivator to promote human lung cancer cell invasion. *J. Clin. Invest., 122*, 1869-80. ↗

O'Malley, BW., Redmond, A., Yuan, Y., Chen, H., Qin, L., Xu, J. et al. (2008). The AIB1 oncogene promotes breast cancer metastasis by activation of PEA3-mediated matrix metalloproteinase 2 (MMP2) and MMP9 expression. *Mol. Cell. Biol., 28*, 5937-50. ↗

Editions

2015-04-03	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
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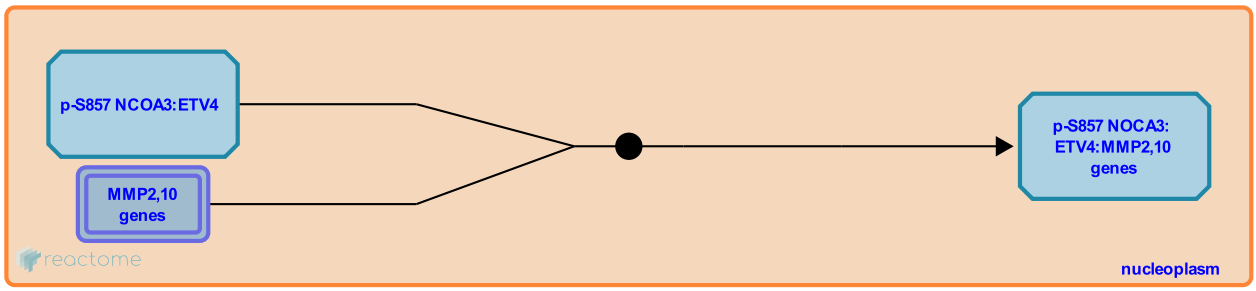
p-S857 NCOA3:ETV4 bind MMP2 and MMP10 promoter ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687099

Type: binding

Compartments: nucleoplasm



MAPK6-dependent phosphorylation of NCOA3 S857 promotes its interaction with the transcription factor ETV4 and increases the occupancy at promoters of the MMP2 and 10 genes in vivo as assessed by ChIP (Long et al, 2012; Qin et al, 2008; Yan et al, 2008). MMP gene expression is associated with invasiveness in lung and breast cancer, and MAPK6 is highly expressed in a subset of human lung carcinomas (Long et al, 2012; Qin et al, 2008; Yan et al, 2008; Li et al, 2008; reviewed in Kostenko et al, 2012).

Preceded by: p-S857 NCOA3 binds ETV4

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Erdem, H., Tsai, SY., Yan, J., Li, R., Tsai, MJ., Ittmann, M. et al. (2008). Steroid receptor coactivator-3/AIB1 promotes cell migration and invasiveness through focal adhesion turnover and matrix metalloproteinase expression. *Cancer Res., 68*, 5460-8. ↗

O'Malley, BW., Foulds, CE., Tsai, SY., Liu, J., Long, W., Tsai, MJ. et al. (2012). ERK3 signals through SRC-3 coactivator to promote human lung cancer cell invasion. *J. Clin. Invest., 122*, 1869-80. ↗

O'Malley, BW., Redmond, A., Yuan, Y., Chen, H., Qin, L., Xu, J. et al. (2008). The AIB1 oncogene promotes breast cancer metastasis by activation of PEA3-mediated matrix metalloproteinase 2 (MMP2) and MMP9 expression. *Mol. Cell. Biol., 28*, 5937-50. ↗

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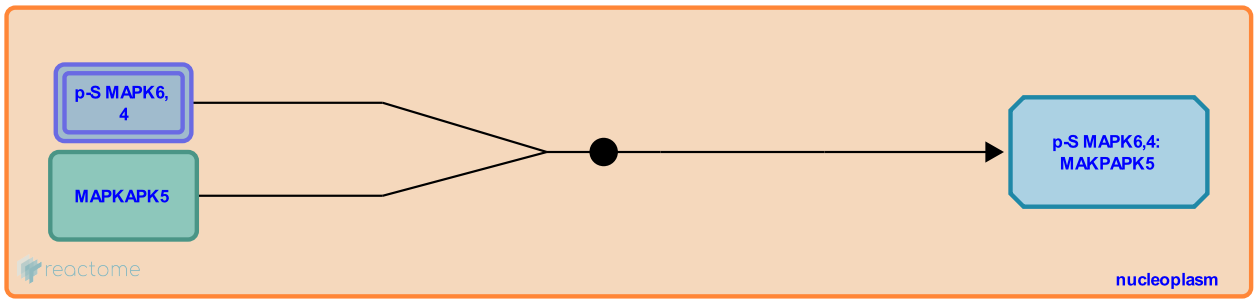
p-S MAPK6,4 binds MAPKAPK5 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687091

Type: binding

Compartments: nucleoplasm



In proliferating cells, p-S189 MAPK6 and pS-186 MAPK4 bind to the MAPK effector kinase MAPKAPK5 (also known as MK5) through an FRIEDE motif in the C-terminal region (Perander et al, 2008; Deleris et al, 2008; Aberg et al, 2009). This motif, which is unique to MAPK6 and MAPK4 binds to the C-terminal 50 residues of MAPKAKP5 and is required for both the cytoplasmic accumulation and the activation of MAPKAPK5 (Aberg et al, 2009; Aberg et al, 2006; Seternes et al, 2004; Deleris et al, 2008). Cytoplasmic redistribution of MAPKAPK5 depends on the protein-protein interaction with MAPK6 or 4 and not the activity of any of the kinases, as cytoplasmic localization is abrogated by disruption of the interaction interface but not by kinase-dead versions of MAPK6, 4 or MAPKAPK5 itself (Aberg et al, 2006; Seternes et al, 2004).

Preceded by: MAPK4,6 translocate to nucleus

Followed by: p-S MAPK6,4 phosphorylate MAPKAPK5

Literature references

Meloche, S., Julien, C., Johansen, B., Aberg, E., Keyse, SM., Perander, M. et al. (2006). Regulation of MAPK-activated protein kinase 5 activity and subcellular localization by the atypical MAPK ERK4/MAPK4. *J. Biol. Chem., 281*, 35499-510. ↗

Déléris, P., Rousseau, J., Meloche, S., Rodier, G., Coulombe, P., Tanguay, PL. (2008). Activation loop phosphorylation of the atypical MAP kinases ERK3 and ERK4 is required for binding, activation and cytoplasmic relocalization of MK5. *J. Cell. Physiol., 217*, 778-88. ↗

Johansen, B., Aberg, E., Torgersen, KM., Perander, M., Keyse, SM., Seternes, OM. (2009). Docking of PRAK/MK5 to the atypical MAPKs ERK3 and ERK4 defines a novel MAPK interaction motif. *J. Biol. Chem., 284*, 19392-401. ↗

Meloche, S., Johansen, B., Morrice, NA., Mikalsen, T., Moens, U., Armstrong, CG. et al. (2004). Activation of MK5/PRAK by the atypical MAP kinase ERK3 defines a novel signal transduction pathway. *EMBO J., 23*, 4780-91. ↗

Johansen, B., Aberg, E., Keyse, SM., Perander, M., Dreyer, B., Guldvik, IJ. et al. (2008). The Ser(186) phospho-acceptor site within ERK4 is essential for its ability to interact with and activate PRAK/MK5. *Biochem. J., 411*, 613-22. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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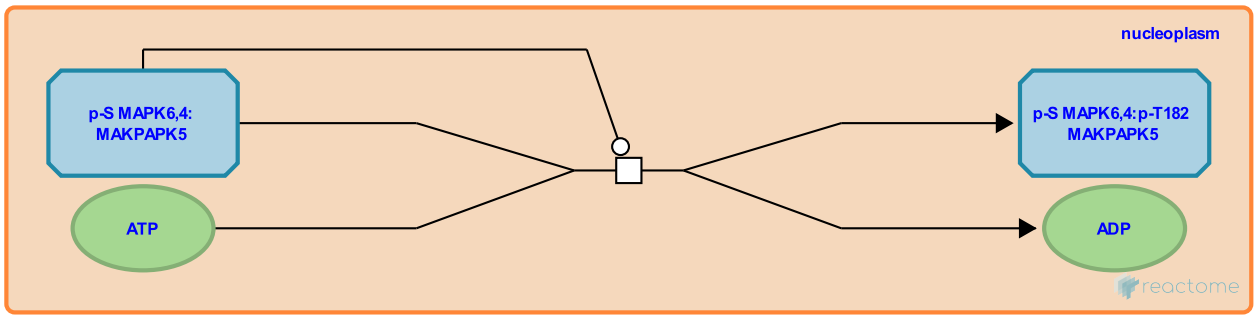
p-S MAPK6,4 phosphorylate MAPKAPK5

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687094

Type: transition

Compartments: nucleoplasm



Activated MAPK6 and MAPK4 promote the phosphorylation of MAPKAPK5 on threonine 182, activating it (Deleris et al, 2008; Aberg et al, 2006; Aberg et al, 2009; Seternes et al, 2004; Perander et al, 2008). Thr182 phosphorylation may result in part from autophosphorylation stimulated by MAPK6 binding, rather than direct phosphorylation by MAPK6, as an ATP-binding pocket mutant of MAPKAKP5 is not phosphorylated in response to MAPK6 (Seternes et al, 2004; Schumacher et al, 2004). There is conflicting evidence as to whether a catalytically inactive MAPK6 mutant can promote MAPKAPK5 phosphorylation (Schumacher et al, 2004; Seternes et al, 2004; Deleris et al, 2008). These conflicting results can be reconciled by the suggestion that inactive MAPK6 promotes MAPKAPK5 phosphorylation through heterodimerization with active MAPK4 (Kant et al, 2006). Phosphorylation of MAPKAPK5 in response to MAPK4/6 signaling promotes its cytoplasmic relocalization (Shumacher et al, 2004; Aberg et al, 2006; Deleris et al, 2008; Seternes et al, 2004).

Preceded by: p-S MAPK6,4 binds MAPKAPK5

Followed by: p-S MAPK6,4:p-T182 MAPKAPK5 translocate to the cytosol

Literature references

Kispert, A., Schumacher, S., Kant, S., Kotlyarov, A., Singh, MK., Gaestel, M. (2006). Characterization of the atypical MAPK ERK4 and its activation of the MAPK-activated protein kinase MK5. *J. Biol. Chem., 281*, 35511-9.

Meloche, S., Julien, C., Johansen, B., Aberg, E., Keyse, SM., Perander, M. et al. (2006). Regulation of MAPK-activated protein kinase 5 activity and subcellular localization by the atypical MAPK ERK4/MAPK4. *J. Biol. Chem., 281*, 35499-510.

Déléris, P., Rousseau, J., Meloche, S., Rodier, G., Coulombe, P., Tanguay, PL. (2008). Activation loop phosphorylation of the atypical MAP kinases ERK3 and ERK4 is required for binding, activation and cytoplasmic relocalization of MK5. *J. Cell. Physiol., 217*, 778-88.

Schumacher, S., Visel, A., Kant, S., Kotlyarov, A., Shi, Y., Gruber, AD. et al. (2004). Scaffolding by ERK3 regulates MK5 in development. *EMBO J., 23*, 4770-9.

Johansen, B., Aberg, E., Torgersen, KM., Perander, M., Keyse, SM., Seternes, OM. (2009). Docking of PRAK/MK5 to the atypical MAPKs ERK3 and ERK4 defines a novel MAPK interaction motif. *J. Biol. Chem., 284*, 19392-401.

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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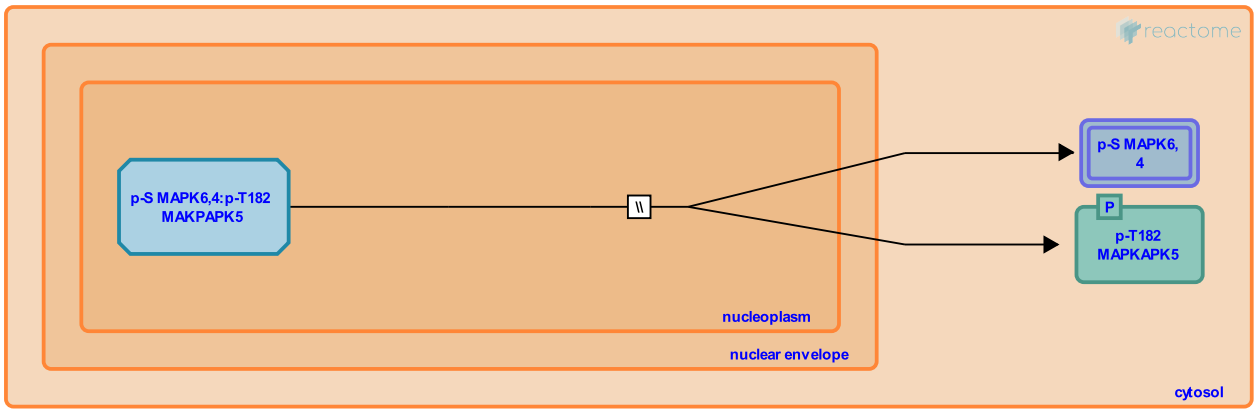
p-S MAPK6,4:p-T182 MAPKAPK5 translocate to the cytosol ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687120

Type: omitted

Compartments: nucleoplasm



Binding of MAPK6 or 4 to MAPKAPK5 promotes its redistribution to the cytosol. This depends on a functional protein-protein interaction interface between the two proteins. Cytoplasmic translocation of MAPKAPK5 occurs even in the presence of catalytically inactive MAPK6 or MAPK6 and vice versa, MAPK6 and MAPK4 still provoke nuclear exclusion of kinase inactive MAPKAPK5 (Aberg et al, 2006; Seternes et al, 2004; Kant et al, 2006; reviewed in Kostenko et al, 2012). Phosphorylation of MAPK6 or MAPK4 at S189 or S186 respectively, is required for binding and translocation of MAPKAPK5 to the cytosol (Perander et al, 2008; Deleris et al, 2008; De La Mota-Peynado et al, 2011).

Preceded by: p-S MAPK6,4 phosphorylate MAPKAPK5

Followed by: p-T182 MAPKAPK5 phosphorylates FOXO3, p-T182 MAPKAPK5 binds DNAJB1, p-S MAPKAPK5 phosphorylates HSPB1

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Kispert, A., Schumacher, S., Kant, S., Kotlyarov, A., Singh, MK., Gaestel, M. (2006). Characterization of the atypical MAPK ERK4 and its activation of the MAPK-activated protein kinase MK5. *J. Biol. Chem., 281*, 35511-9. ↗

Meloche, S., Julien, C., Johansen, B., Aberg, E., Keyse, SM., Perander, M. et al. (2006). Regulation of MAPK-activated protein kinase 5 activity and subcellular localization by the atypical MAPK ERK4/MAPK4. *J. Biol. Chem., 281*, 35499-510. ↗

De la Mota-Peynado, A., Beeser, A., Chernoff, J. (2011). Identification of the atypical MAPK Erk3 as a novel substrate for p21-activated kinase (Pak) activity. *J. Biol. Chem., 286*, 13603-11. ↗

Déléris, P., Rousseau, J., Meloche, S., Rodier, G., Coulombe, P., Tanguay, PL. (2008). Activation loop phosphorylation of the atypical MAP kinases ERK3 and ERK4 is required for binding, activation and cytoplasmic relocalization of MK5. *J. Cell. Physiol., 217*, 778-88. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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2015-05-13	Edited	Rothfels, K.

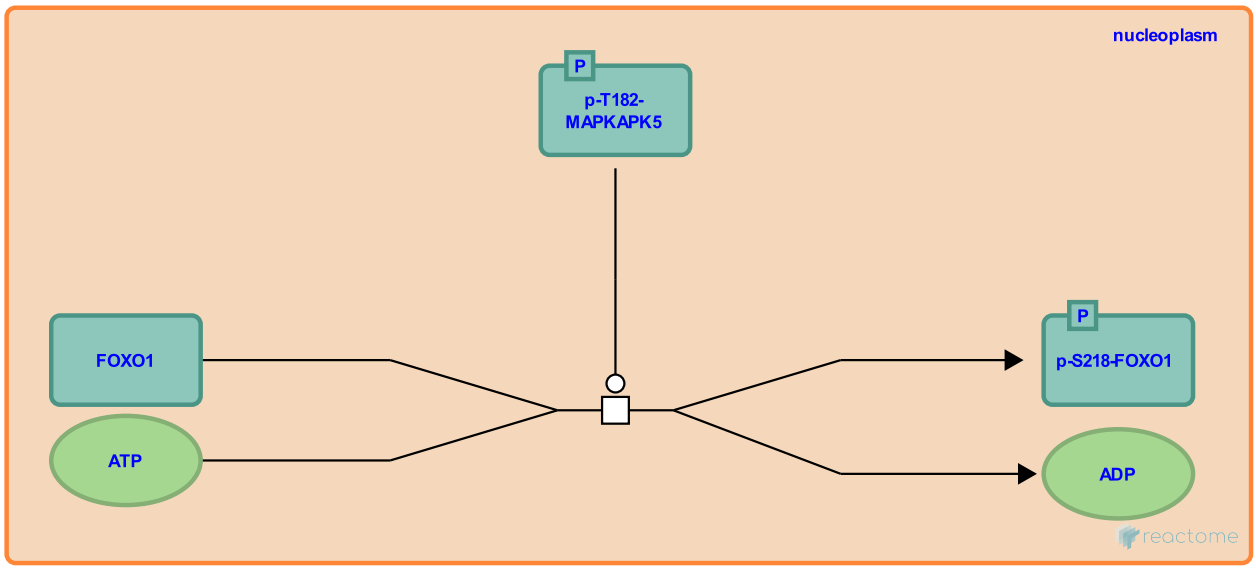
p-T182 MAPKAPK5 phosphorylates FOXO1 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692779

Type: transition

Compartments: nucleoplasm



MAPKAPK5 phosphorylates FOXO1 at S218 (corresponds to S215 in mouse Foxo1). This phosphorylation is essential for the FOXO1-dependent activation of RAG gene transcription during B-cell development and promotes the direct binding of FOXO1 to the RAG gene promoter (Chow et al, 2013).

Literature references

Chow, KT., Timblin, GA., McWhirter, SM., Schlissel, MS. (2013). MK5 activates Rag transcription via Foxo1 in developing B cells. *J. Exp. Med., 210*, 1621-34. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
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2015-05-13	Edited	Rothfels, K.

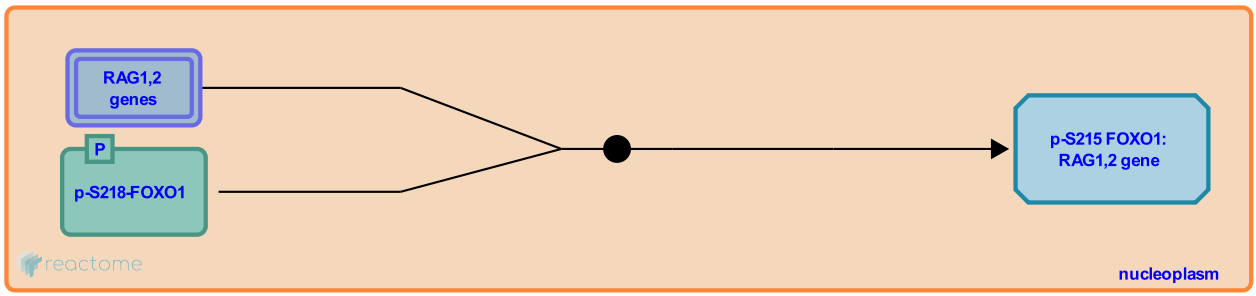
p-S215 FOXO1 binds RAG gene ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692785

Type: binding

Compartments: nucleoplasm



After phosphorylation by MAPKAPK5, p-S218 FOXO1 binds to the RAG gene promoter to promote transcription (Lin et al, 2010; Ochiai et al, 2012; Chow et al, 2013).

Literature references

Benner, C., Glass, CK., Murre, C., Hagman, J., Heinz, S., Mansson, R. et al. (2010). A global network of transcription factors, involving E2A, EBF1 and Foxo1, that orchestrates B cell fate. *Nat. Immunol., 11*, 635-43. ↗

Chow, KT., Timblin, GA., McWhirter, SM., Schlissel, MS. (2013). MK5 activates Rag transcription via Foxo1 in developing B cells. *J. Exp. Med., 210*, 1621-34. ↗

Bertolino, E., Mandal, M., Singh, H., Triggs, JR., Ochiai, K., Dinner, AR. et al. (2012). A self-reinforcing regulatory network triggered by limiting IL-7 activates pre-BCR signaling and differentiation. *Nat. Immunol., 13*, 300-7. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
2015-05-12	Authored, Reviewed	Meloche, S., Soulez, M.
2015-05-13	Edited	Rothfels, K.

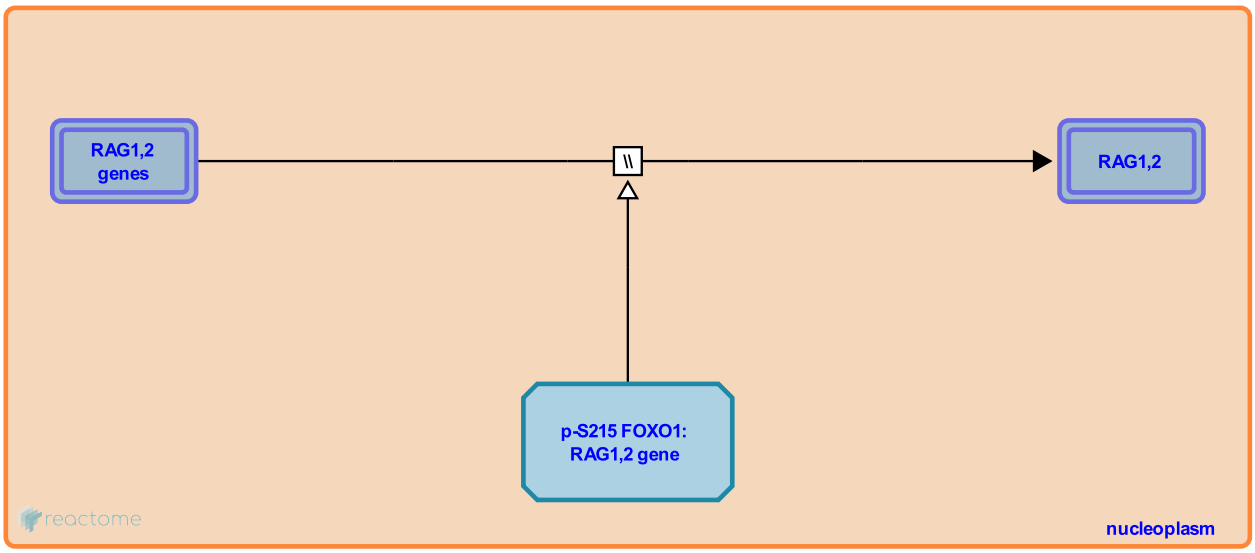
p-S215 FOXO1 positively regulates RAG gene expression ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692794

Type: omitted

Compartments: nucleoplasm



Binding of p-S215 FOXO1 to the RAG genes promotes expression of RAG proteins, which are required for V(D)J recombination (Chow et al, 2013).

Literature references

Chow, KT., Timblin, GA., McWhirter, SM., Schlissel, MS. (2013). MK5 activates Rag transcription via Foxo1 in developing B cells. *J. Exp. Med., 210*, 1621-34. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
2015-05-12	Authored, Reviewed	Meloche, S., Soulez, M.
2015-05-13	Edited	Rothfels, K.

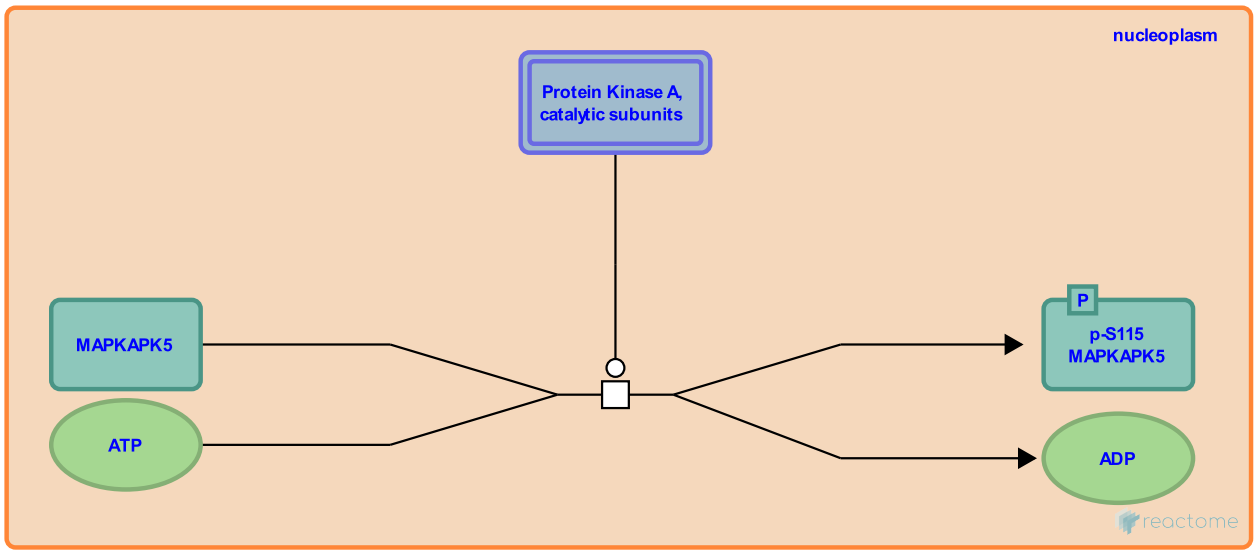
PKA phosphorylates MAPKAPK5

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687088

Type: transition

Compartments: nucleoplasm



MAPKAPK5 is phosphorylated at serine 115 by the catalytic subunit of PKA, which translocates into the nucleus in response to elevated cellular cAMP levels. Phosphorylation at serine 115 promotes the cytoplasmic relocalization of MAPKAPK5 and is required for HSBP1-dependent rearrangements of F-actin in response to PKA (Gerits et al, 2007; Kostenko et al, 2011a; Kostenko et al, 2009; reviewed in Kostenko et al, 2011b)

Followed by: p-S115 MAPKAPK5 translocates to the cytosol

Literature references

Dumitriu, G., Kostenko, S., Moens, U., Gerits, N., Shiryaev, A. (2011). Cross-talk between protein kinase A and the MAPK-activated protein kinases RSK1 and MK5. *J. Recept. Signal Transduct. Res., 31*, 1-9.

Dumitriu, G., Klenow, H., Kostenko, S., Moens, U., Johannessen, M., Gerits, N. et al. (2011). Serine residue 115 of MAPK-activated protein kinase MK5 is crucial for its PKA-regulated nuclear export and biological function. *Cell. Mol. Life Sci., 68*, 847-62.

Kostenko, S., Mikalsen, T., Moens, U., Johannessen, M., Gerits, N., Shiryaev, A. (2007). Modulation of F-actin re-arrangement by the cyclic AMP/cAMP-dependent protein kinase (PKA) pathway is mediated by MAPK-activated protein kinase 5 and requires PKA-induced nuclear export of MK5. *J. Biol. Chem., 282*, 37232-43.

Kostenko, S., Moens, U., Johannessen, M. (2009). PKA-induced F-actin rearrangement requires phosphorylation of Hsp27 by the MAPKAP kinase MK5. *Cell. Signal., 21*, 712-8.

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2015-04-03	Authored	Rothfels, K.
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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

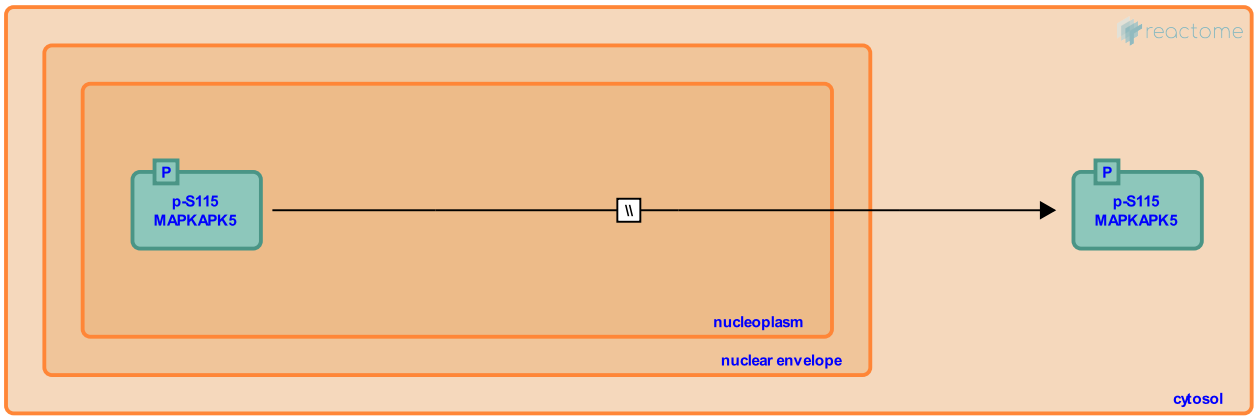
p-S115 MAPKAPK5 translocates to the cytosol ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687123

Type: omitted

Compartments: nucleoplasm



PKA-mediated phosphorylation of serine 115 promotes the translocation of MAPKAPK5 to the cytosol (Kostenko et al, 2011a; Gerits et al, 2007).

Preceded by: PKA phosphorylates MAPKAPK5

Followed by: p-S MAPKAPK5 phosphorylates HSPB1

Literature references

Dumitriu, G., Klenow, H., Kostenko, S., Moens, U., Johannessen, M., Gerits, N. et al. (2011). Serine residue 115 of MAPK-activated protein kinase MK5 is crucial for its PKA-regulated nuclear export and biological function. *Cell. Mol. Life Sci., 68*, 847-62. ↗

Kostenko, S., Mikalsen, T., Moens, U., Johannessen, M., Gerits, N., Shiryaev, A. (2007). Modulation of F-actin rearrangement by the cyclic AMP/cAMP-dependent protein kinase (PKA) pathway is mediated by MAPK-activated protein kinase 5 and requires PKA-induced nuclear export of MK5. *J. Biol. Chem., 282*, 37232-43. ↗

Editions

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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

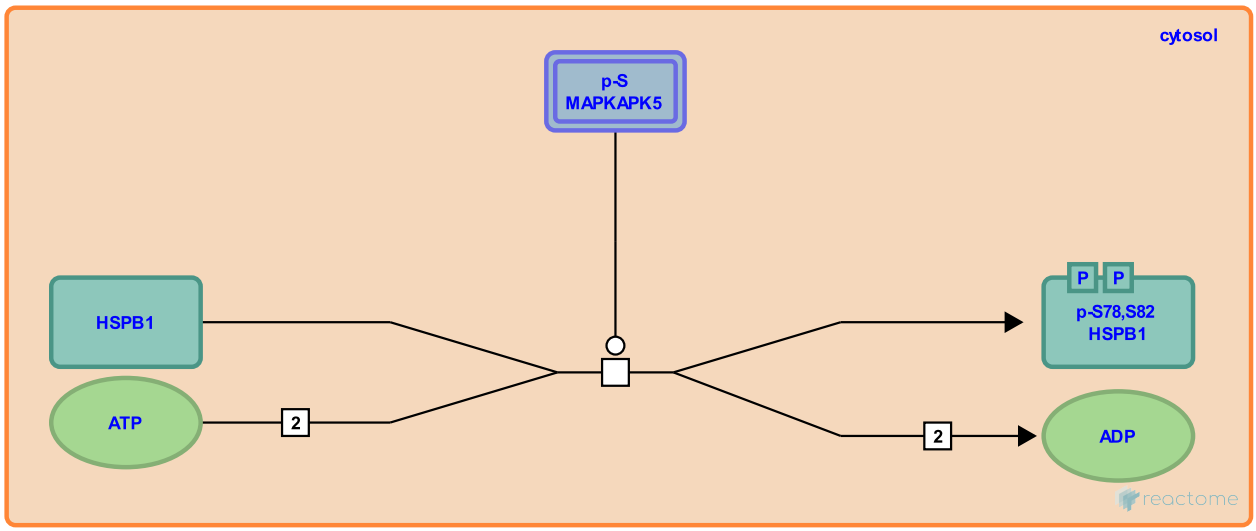
p-S MAPKAPK5 phosphorylates HSPB1 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687121

Type: transition

Compartments: cytosol



HSBP1, also known as HSP27, is small actin-binding protein with roles in cytoskeletal regulation as well as other processes. HSBP1 is a substrate for MAPKAPK5 both in vitro and in vivo, and phosphorylation of serine residues stimulates forskolin-induced F-actin rearrangements (Sun et al, 2007; Tak et al, 2007; Gerits et al, 2007; New et al, 1998; Seternes et al, 2004; Kostenko et al, 2009a; Kostenko et al, 2009b; Kostenko et al, 2011a; reviewed in Kostenko et al, 2011b; Kostenko et al, 2012). There are divergent reports about the physiological relevance of HSBP1 phosphorylation on actin polymeriztion and cell motility (Lavoie et al, 1995; Lamalice et al, 2007; Katsogiannou et al, 2014; Rousseau et al, 2000; Doshi et al, 2010; Stohr et al, 2012). Actin cytoskeletal rearrangements through the MAPK4 pathway are controlled in part by the IGF2BP1-mediated downregulation of MAPK4 translation which abrogates MAPKAPK5 activity and HSBP1 phosphorylation (Stohr et al, 2012).

Preceded by: p-S MAPK6,4:p-T182 MAPKAPK5 translocate to the cytosol, p-S115 MAPKAPK5 translocates to the cytosol

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Andrieu, C., Katsogiannou, M., Rocchi, P. (2014). Heat shock protein 27 phosphorylation state is associated with cancer progression. *Front Genet, 5*, 346. ↗

Weber, LA., Lavoie, JN., Lambert, H., Landry, J., Hickey, E. (1995). Modulation of cellular thermoresistance and actin filament stability accompanies phosphorylation-induced changes in the oligomeric structure of heat shock protein 27. *Mol. Cell. Biol., 15*, 505-16. ↗

Dumitriu, G., Klenow, H., Kostenko, S., Moens, U., Johannessen, M., Gerits, N. et al. (2011). Serine residue 115 of MAPK-activated protein kinase MK5 is crucial for its PKA-regulated nuclear export and biological function. *Cell. Mol. Life Sci., 68*, 847-62. ↗

Li, Y., Yamout, M., Sun, P., Frangou, CG., Yates, JR., Liao, R. et al. (2007). PRAK is essential for ras-induced senescence and tumor suppression. *Cell, 128*, 295-308. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

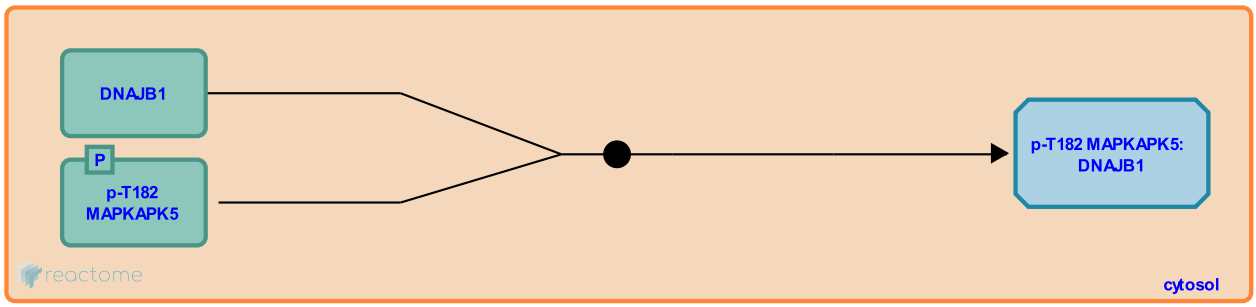
p-T182 MAPKAPK5 binds DNAJB1 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5690245

Type: binding

Compartments: cytosol



Cytosolic MAPKAPK5 forms a complex with DNAJB1 through an interaction mediated by the C-terminal tails of both proteins (Kostenko et al, 2014).

Preceded by: p-S MAPK6,4:p-T182 MAPKAPK5 translocate to the cytosol

Followed by: p-T182-MAPKAPK5 phoshphorylates DNAJB1

Literature references

Jensen, KL., Kostenko, S., Moens, U. (2014). Phosphorylation of heat shock protein 40 (Hsp40/DnaJB1) by mitogen-activated protein kinase-activated protein kinase 5 (MK5/PRAK). *Int. J. Biochem. Cell Biol., 47*, 29-37. ↗

Editions

2015-04-24	Authored, Reviewed	Moens, U.
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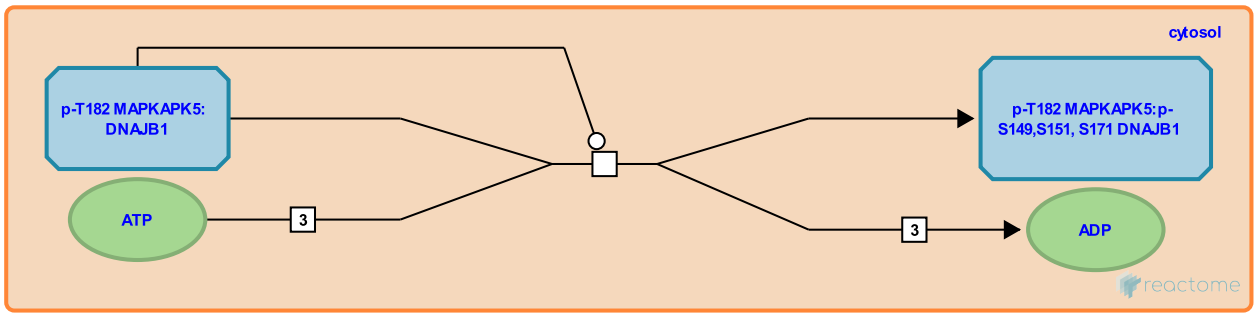
p-T182-MAPKAPK5 phoshphorylates DNAJB1 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5690250

Type: transition

Compartments: cytosol



Activated MAPKAPK5 phosphorylates HSP40/DNAJB1 at serines 149, 151 and 171, promoting the ATP hydrolysis activity of the HSP40/HSP70 complex and enhancing the repression of heat shock factor 1 (HSF1) driven transcription by HSP40/DNAJB1 (Kostenko et al, 2014).

Preceded by: p-T182 MAPKAPK5 binds DNAJB1

Literature references

Jensen, KL., Kostenko, S., Moens, U. (2014). Phosphorylation of heat shock protein 40 (Hsp40/DnaJB1) by mitogen-activated protein kinase-activated protein kinase 5 (MK5/PRAK). *Int. J. Biochem. Cell Biol., 47*, 29-37. ↗

Editions

2015-04-24	Authored, Reviewed	Moens, U.
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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

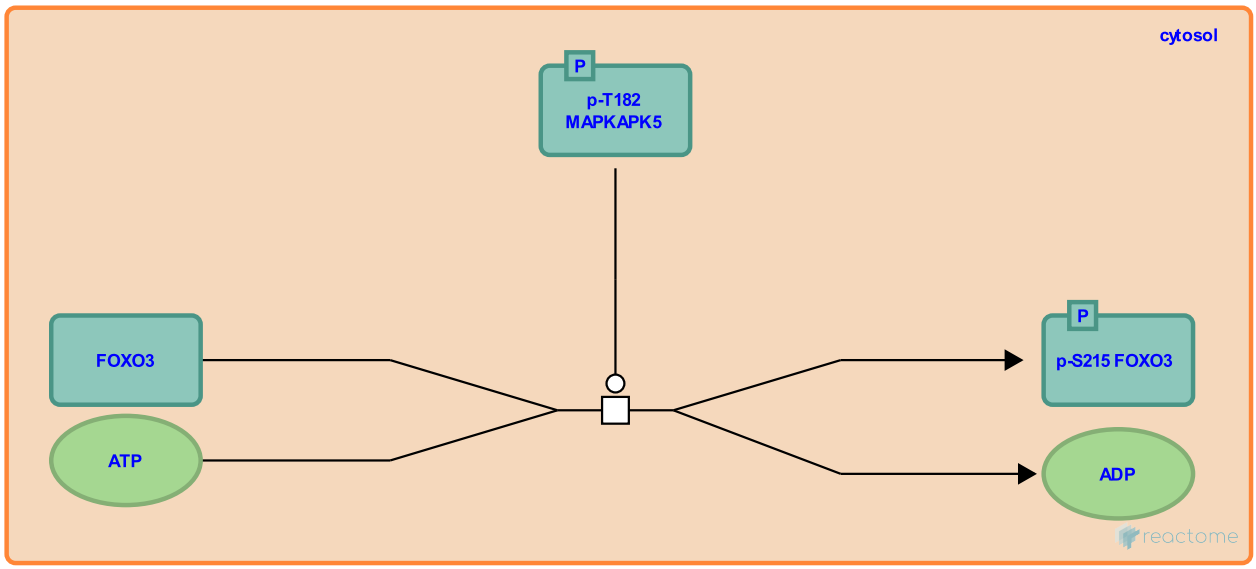
p-T182 MAPKAPK5 phosphorylates FOXO3 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687101

Type: transition

Compartments: cytosol



Activated MAPKAPK5 phosphorylates FOXO3 at serine 215, promoting its activation and translocation to the nucleus. In the nucleus, FOXO3 promotes the expression of miR-34B and C, which in turn represses translation of MYC RNA (Kress et al, 2011; reviewed in Myant and Sansom, 2011; Kostenko et al, 2012).

Preceded by: p-S MAPK6,4:p-T182 MAPKAPK5 translocate to the cytosol

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Kress, TR., Eilers, M., Roepman, P., Bushell, M., Samans, B., Cannell, IG. et al. (2011). The MK5/PRAK kinase and Myc form a negative feedback loop that is disrupted during colorectal tumorigenesis. *Mol. Cell, 41*, 445-57. ↗

Myant, K., Sansom, OJ. (2011). More, more, more: downregulation of a MK5-FoxO3a-mir34b/c pathway further increases c-Myc levels in colorectal cancer. *Mol. Cell, 41*, 369-70. ↗

Editions

2015-03-30	Authored	Rothfels, K.
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2015-05-13	Edited	Rothfels, K.

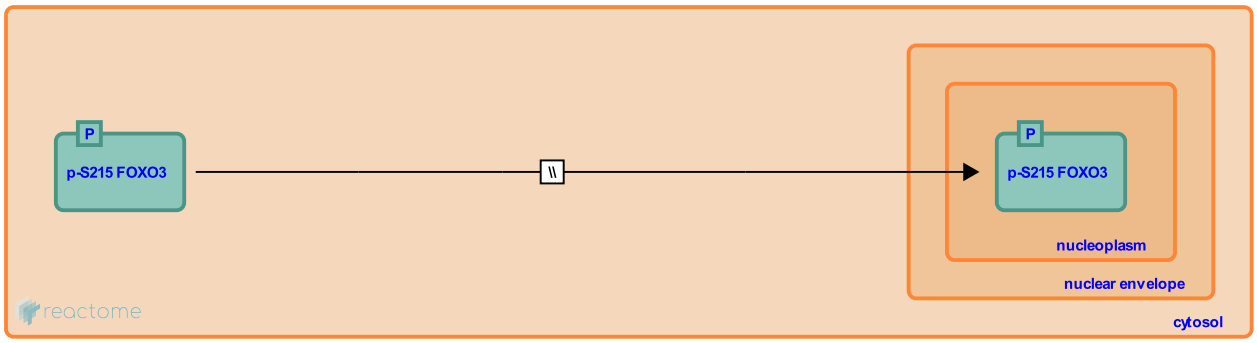
p-S215 FOXO3 translocates to the nucleus ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687126

Type: omitted

Compartments: cytosol



MAPKAPK5-dependent phosphorylation of FOXO3 promotes its nuclear localization (Kress et al, 2011). In the nucleus, FOXO3 promotes expression of miR-34B and C and thereby downregulates expression of c-MYC RNA (Kress et al, 2011; reviewed in Myant and Sansom, 2011; Kostenko et al, 2012).

Followed by: p-S215 FOXO3 binds MIR34B and C gene

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Kress, TR., Eilers, M., Roepman, P., Bushell, M., Samans, B., Cannell, IG. et al. (2011). The MK5/PRAK kinase and Myc form a negative feedback loop that is disrupted during colorectal tumorigenesis. *Mol. Cell, 41*, 445-57. ↗

Myant, K., Sansom, OJ. (2011). More, more, more: downregulation of a MK5-FoxO3a-mir34b/c pathway further increases c-Myc levels in colorectal cancer. *Mol. Cell, 41*, 369-70. ↗

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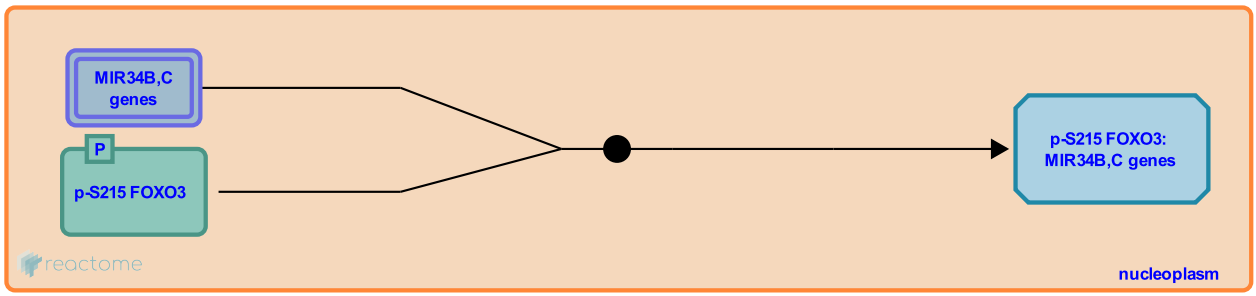
p-S215 FOXO3 binds MIR34B and C gene ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687095

Type: binding

Compartments: nucleoplasm



Phosphorylated FOXO3 binds to consensus sites in the promoter of MIR34B and C genes as assessed by ChIP, promoting expression of the microRNAs (Kress et al, 2011).

Preceded by: p-S215 FOXO3 translocates to the nucleus

Literature references

Kress, TR., Eilers, M., Roepman, P., Bushell, M., Samans, B., Cannell, IG. et al. (2011). The MK5/PRAK kinase and Myc form a negative feedback loop that is disrupted during colorectal tumorigenesis. *Mol. Cell, 41*, 445-57. ↗

Editions

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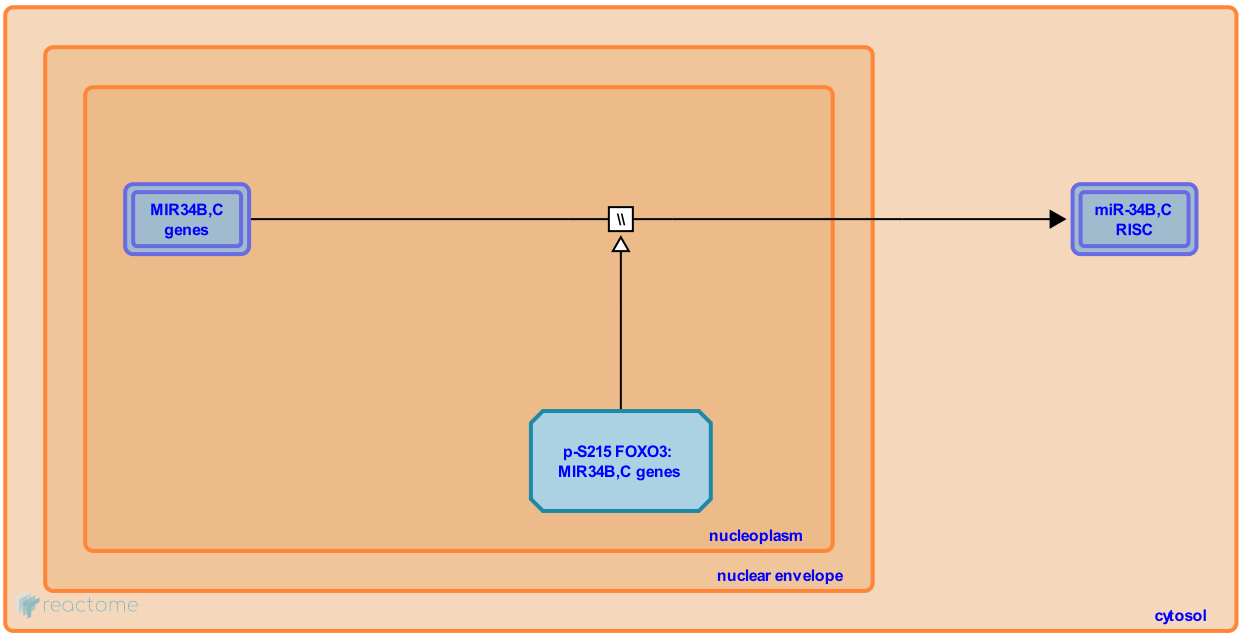
FOXO3 regulates MIR34B,C expression ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687103

Type: omitted

Compartments: nucleoplasm



p-S215 FOXO3 binds to the promoter of the MIR34B and C gene and promotes its expression (Kress et al, 2011).

Literature references

Kress, TR., Eilers, M., Roepman, P., Bushell, M., Samans, B., Cannell, IG. et al. (2011). The MK5/PRAK kinase and Myc form a negative feedback loop that is disrupted during colorectal tumorigenesis. *Mol. Cell, 41*, 445-57. ↗

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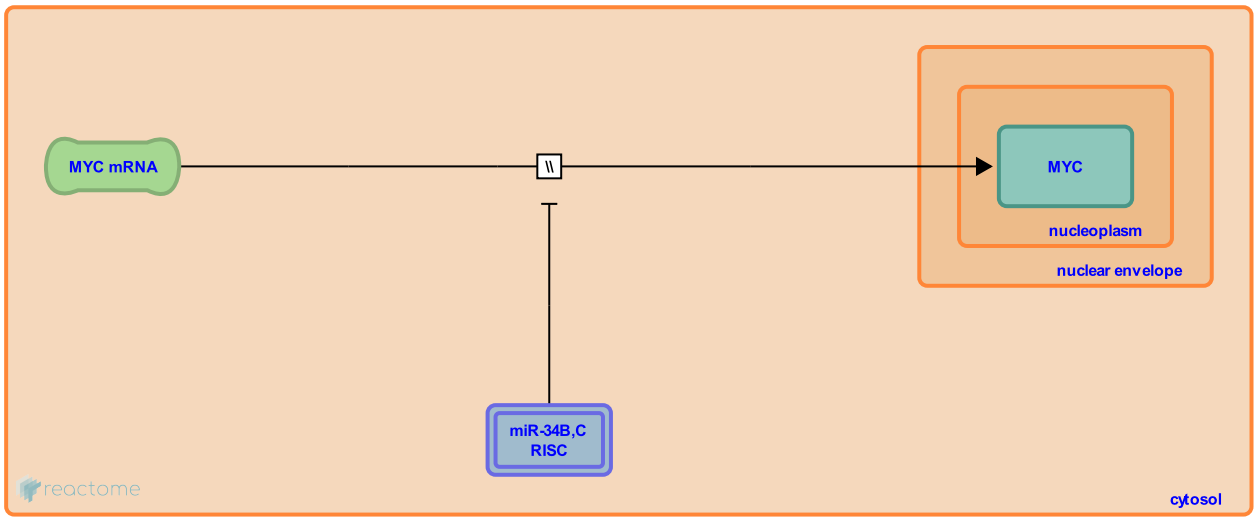
MYC mRNA translation is negatively regulated by miR-34B and C ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687113

Type: omitted

Compartments: cytosol



Translation of MYC mRNA is negatively regulated by miR-34B and C microRNAs (Kress et al, 2011). miR-34 miRNAs bind and cause degradation of MYC mRNA, resulting in decreased level of MYC protein product (reviewed in Myant and Sansom, 2011; Kostenko et al, 2012).

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Kress, TR., Eilers, M., Roepman, P., Bushell, M., Samans, B., Cannell, IG. et al. (2011). The MK5/PRAK kinase and Myc form a negative feedback loop that is disrupted during colorectal tumorigenesis. *Mol. Cell, 41*, 445-57. ↗

Myant, K., Sansom, OJ. (2011). More, more, more: downregulation of a MK5-FoxO3a-mir34b/c pathway further increases c-Myc levels in colorectal cancer. *Mol. Cell, 41*, 369-70. ↗

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2015-05-13	Edited	Rothfels, K.

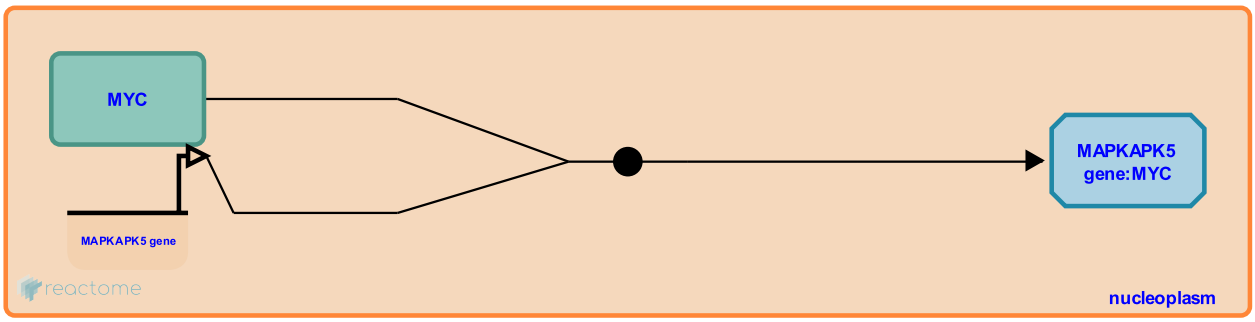
MYC binds MAPKAPK5 gene ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687083

Type: binding

Compartments: nucleoplasm



MYC binds to consensus sites in the MAPKAPK5 gene promoter as assessed by ChIP (Kress et al, 2011). Although not depicted here and not experimentally validated in this context, MYC likely binds the promoter in the context of a MYC:MAX heterodimer.

Literature references

Kress, TR., Eilers, M., Roepman, P., Bushell, M., Samans, B., Cannell, IG. et al. (2011). The MK5/PRAK kinase and Myc form a negative feedback loop that is disrupted during colorectal tumorigenesis. *Mol. Cell, 41*, 445-57. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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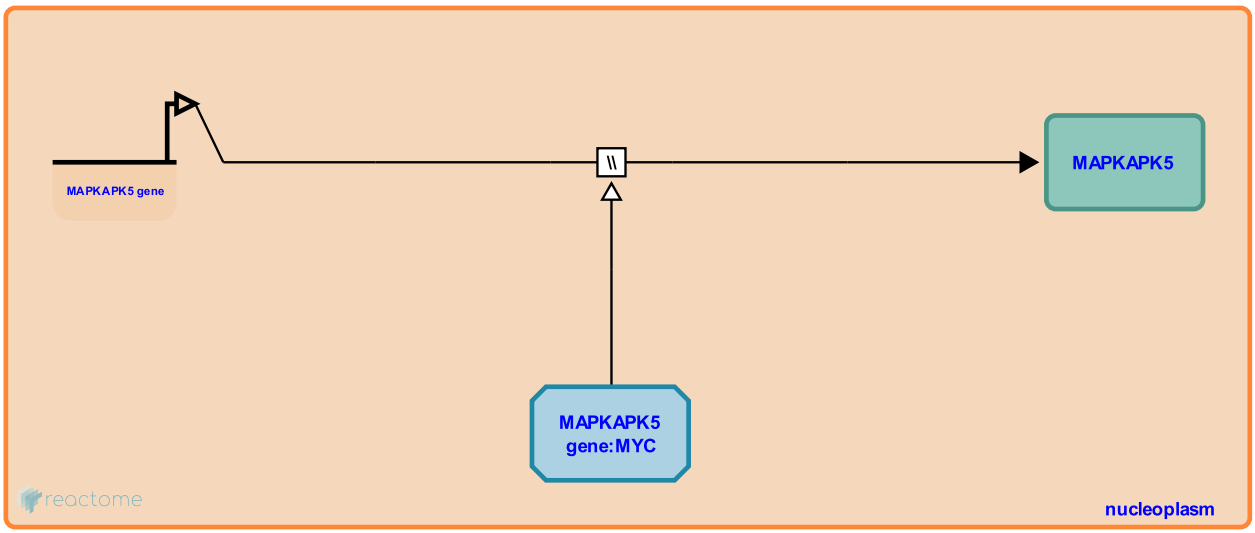
MYC positively regulates MAPKAPK5 gene expression ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687115

Type: omitted

Compartments: nucleoplasm



MYC binds to consensus sites in the MAPKAPK5 promoter to promote transcription. This completes a negative feedback loop controlling MYC expression, as MAPKAPK5 itself negatively regulates MYC protein levels through FOXO3 and miR-34B and C (Kress et al, 2011). This pathway is disrupted in colorectal cancer, leading to aberrant cellular proliferation (Kress et al, 2011; reviewed in Myant and Sansom, 2011; Kostenko et al, 2012).

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Kress, TR., Eilers, M., Roepman, P., Bushell, M., Samans, B., Cannell, IG. et al. (2011). The MK5/PRAK kinase and Myc form a negative feedback loop that is disrupted during colorectal tumorigenesis. *Mol. Cell, 41*, 445-57. ↗

Myant, K., Sansom, OJ. (2011). More, more, more: downregulation of a MK5-FoxO3a-mir34b/c pathway further increases c-Myc levels in colorectal cancer. *Mol. Cell, 41*, 369-70. ↗

Editions

2015-03-30	Authored	Rothfels, K.
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2015-05-12	Reviewed	Meloche, S., Soulez, M., Mathien, S.
2015-05-13	Edited	Rothfels, K.

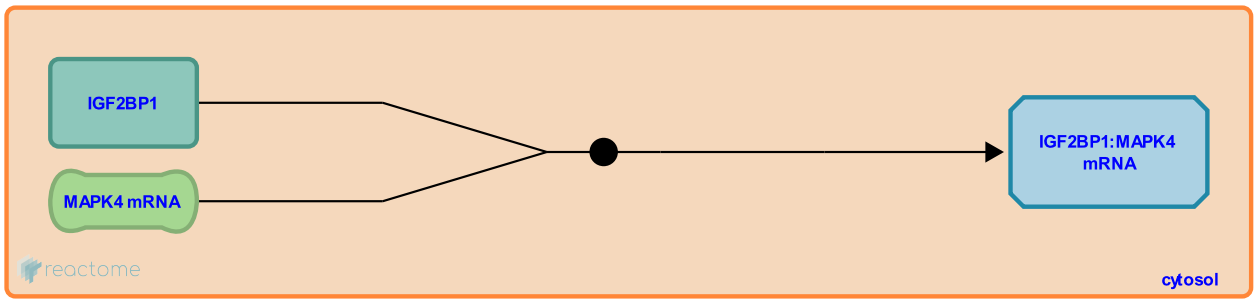
IGF2BP1 binds MAPK4 mRNA ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687079

Type: binding

Compartments: cytosol



IGF2BP1 is a cytosolic RNA-binding protein that recruits target transcripts to RNP particles for storage or transport. These RNP particles also restrict access of the translational machinery and micro-RNAs to the transcript and in this way affect rates of protein translation (reviewed in Bell et al, 2013). IGFBP1 binds to the 3' UTR of MAPK4 mRNA and inhibits its translation. This antagonizes MAPKAPK5 activation and HSBP1 phosphorylation and in this manner affects F-actin rearrangements and cell motility (Stohr et al, 2012; Kostenko et al, 2009a; reviewed in Kostenko et al, 2012).

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Bell, JL., Pazaitis, N., Mühleck, B., Wächter, K., Lederer, M., Hüttelmaier, S. et al. (2013). Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs): post-transcriptional drivers of cancer progression?. *Cell. Mol. Life Sci., 70*, 2657-75. ↗

Kostenko, S., Moens, U., Johannessen, M. (2009). PKA-induced F-actin rearrangement requires phosphorylation of Hsp27 by the MAPKAP kinase MK5. *Cell. Signal., 21*, 712-8. ↗

Glass, M., Stöhr, N., Lederer, M., Singer, RH., Hüttelmaier, S., Reinke, C. et al. (2012). IGF2BP1 promotes cell migration by regulating MK5 and PTEN signaling. *Genes Dev., 26*, 176-89. ↗

Editions

2015-03-30	Authored	Rothfels, K.
2015-04-24	Reviewed	Moens, U.
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2015-05-13	Edited	Rothfels, K.

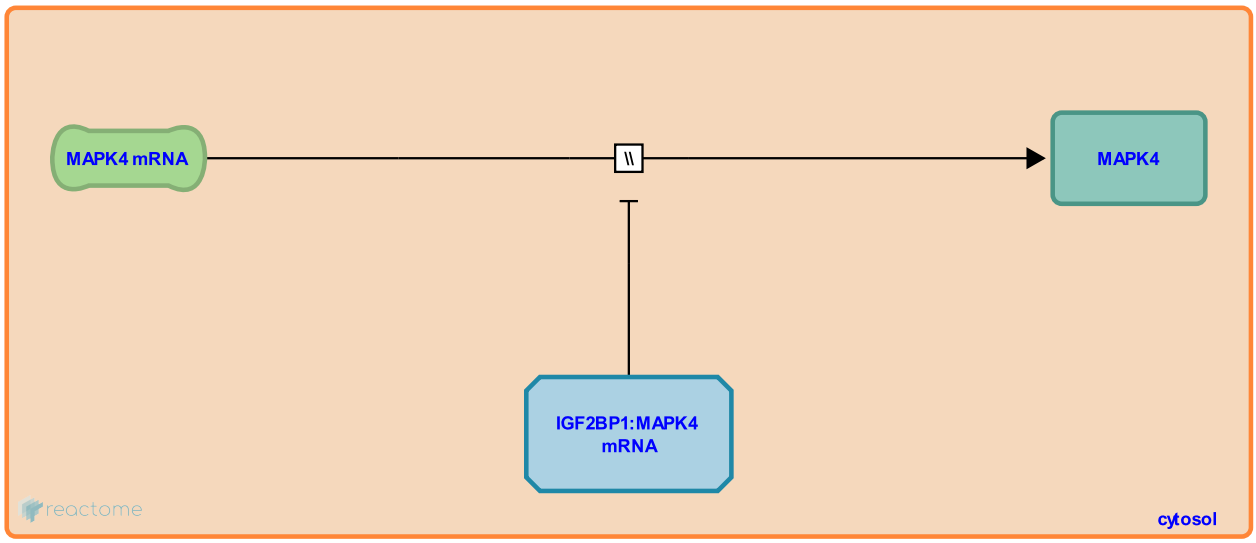
IGF2BP1 represses translation of MAPK4 mRNA ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5687105

Type: omitted

Compartments: cytosol



Binding of IGF2BP1 to the 3' UTR of MAPK4 mRNA inhibits its translation and in this way antagonizes the MAPKAPK5-dependent phosphorylation of HSBP1 (Stohr et al, 2012; Kostenko et al, 2009a; reviewed in Kostenko et al, 2012).

Literature references

Dumitriu, G., Kostenko, S., Moens, U. (2012). Tumour promoting and suppressing roles of the atypical MAP kinase signalling pathway ERK3/4-MK5. *J Mol Signal, 7*, 9. ↗

Kostenko, S., Moens, U., Johannessen, M. (2009). PKA-induced F-actin rearrangement requires phosphorylation of Hsp27 by the MAPKAP kinase MK5. *Cell. Signal., 21*, 712-8. ↗

Glass, M., Stöhr, N., Lederer, M., Singer, RH., Hüttelmaier, S., Reinke, C. et al. (2012). IGF2BP1 promotes cell migration by regulating MK5 and PTEN signaling. *Genes Dev., 26*, 176-89. ↗

Editions

2015-03-30	Authored	Rothfels, K.
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2015-05-13	Edited	Rothfels, K.

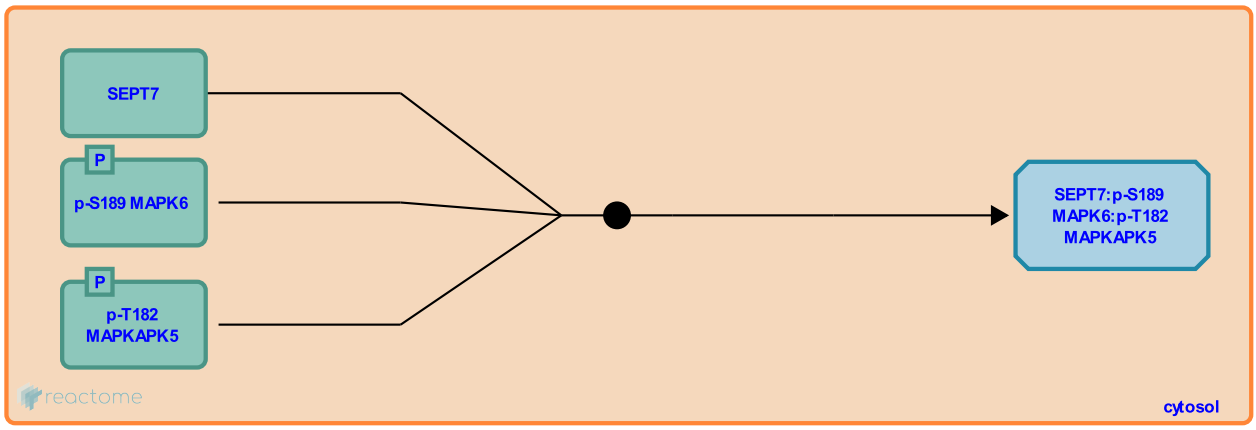
SEPT7 binds p-S189 MAPK6 and p-T182 MAPKAPK5 ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692770

Type: binding

Compartments: cytosol



SEPT7 forms a ternary complex with MAPK6 and MAPKAPK5 that contributes to neuronal development through the phosphorylation of the Binders of RHO GTPase (BORG) proteins (Brand et al, 2012). Septins are cytoskeletal GTP-binding proteins that form filaments and contribute to processes such as cytokinesis, cell polarity and cell division, among others (reviewed in Spiliotis and Nelson, 2006). Interaction of septin proteins with the CDC42 effector proteins 2, 3 and 5 (CDC42EP2, 3, 5; also known as BORG1, 2 and 3) inhibits formation of septin filaments (Jouberty et al, 2001).

Literature references

Perlungher, RR., Joberty, G., Macara, IG., Kinoshita, M., Sheffield, PJ., Haystead, T. et al. (2001). Borg proteins control septin organization and are negatively regulated by Cdc42. *Nat. Cell Biol., 3*, 861-6. ↗

Spiliotis, ET., Nelson, WJ. (2006). Here come the septins: novel polymers that coordinate intracellular functions and organization. *J. Cell. Sci., 119*, 4-10. ↗

Schumacher, S., Brand, F., Kant, S., Meloche, S., Kotlyarov, A., Gaestel, M. et al. (2012). The extracellular signal-regulated kinase 3 (mitogen-activated protein kinase 6 [MAPK6])-MAPK-activated protein kinase 5 signaling complex regulates septin function and dendrite morphology. *Mol. Cell. Biol., 32*, 2467-78. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
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2015-05-13	Edited	Rothfels, K.

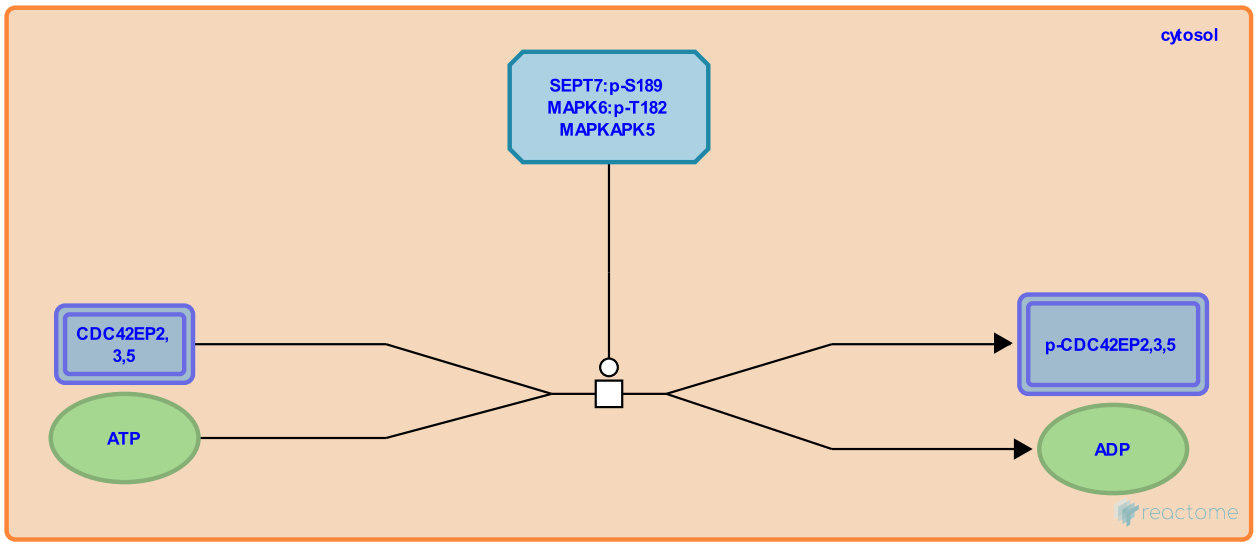
SEPT7:p-S189 MAPK6:p-T182 MAPKAPK5 phosphorylates CDC42EPs ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692775

Type: transition

Compartments: cytosol



MAPK6 and MAPKAPK5 directly phosphorylate the septin regulating proteins CDC42EP2, 3 and 5 (also known as BORG1, 2 and 3 for Binders of Rho GTPases) in vitro. BORG/CDC42EP proteins interact with septins through the septin GTPase domain and inhibit filament formation. This effect of the BORG proteins on septin filamentation is itself inhibited by CDC42 (Jouberty et al, 2001; reviewed in Spiliotis and Nelson, 2006). The interaction between SEPT7 and the CDC42EP proteins may facilitate their recruitment to the ternary MAPK6:MAPKAPK5:SEPT7 complex for phosphorylation, although the significance of this phosphorylation is not yet clear (Brand et al, 2012).

Literature references

Perlungher, RR., Joberty, G., Macara, IG., Kinoshita, M., Sheffield, PJ., Haystead, T. et al. (2001). Borg proteins control septin organization and are negatively regulated by Cdc42. *Nat. Cell Biol., 3*, 861-6. ↗

Spiliotis, ET., Nelson, WJ. (2006). Here come the septins: novel polymers that coordinate intracellular functions and organization. *J. Cell. Sci., 119*, 4-10. ↗

Schumacher, S., Brand, F., Kant, S., Meloche, S., Kotlyarov, A., Gaestel, M. et al. (2012). The extracellular signal-regulated kinase 3 (mitogen-activated protein kinase 6 [MAPK6])-MAPK-activated protein kinase 5 signaling complex regulates septin function and dendrite morphology. *Mol. Cell. Biol., 32*, 2467-78. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
2015-05-12	Authored, Reviewed	Meloche, S., Soulez, M.
2015-05-13	Edited	Rothfels, K.

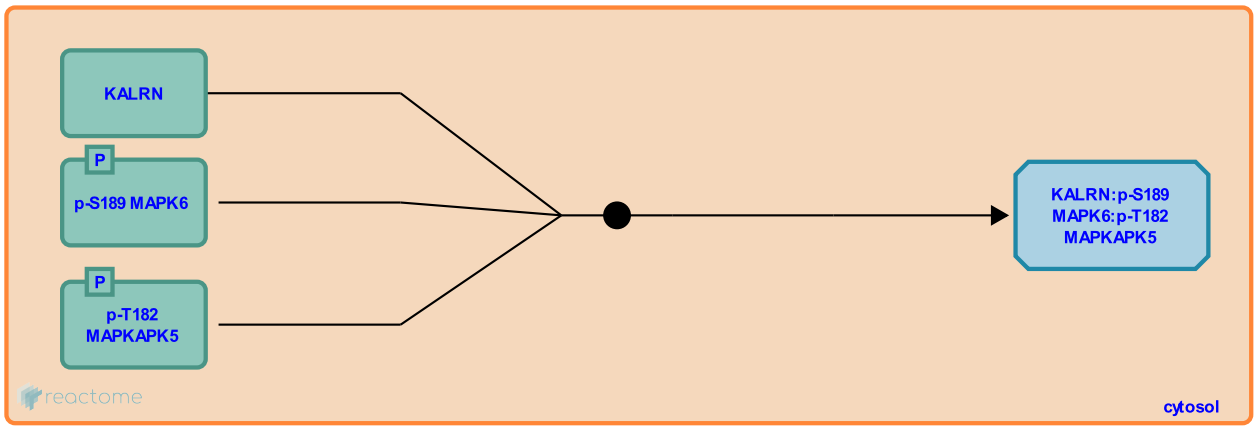
p-S189 MAPK6:p-T182 MAPKAPK5 bind KALRN ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692781

Type: binding

Compartments: cytosol



MAPK6 and MAPKAPK5 bind to the GDP-exchange factor KALRN, also known as Kalirin-7 or KAL7 (Brand et al, 2012). CaMKII-dependent phosphorylation of KALRN7 results in activation of PAK kinases in dendritic spines, potentially establishing a positive feedback loop that governs the MAPK6:MAPKAPK5 module in neuronal developement (Penzes et al, 2003; Xie et al, 2007).

Literature references

Penzes, P., Kai, L., Surmeier, DJ., Photowala, H., Cahill, ME., Srivastava, DP. et al. (2007). Kalirin-7 controls activity-dependent structural and functional plasticity of dendritic spines. *Neuron, 56*, 640-56. ↗

Penzes, P., Eipper, BA., Schiller, MR., Huganir, RL., Chernoff, J., Beeser, A. et al. (2003). Rapid induction of dendritic spine morphogenesis by trans-synaptic ephrinB-EphB receptor activation of the Rho-GEF kalirin. *Neuron, 37*, 263-74. ↗

Schumacher, S., Brand, F., Kant, S., Meloche, S., Kotlyarov, A., Gaestel, M. et al. (2012). The extracellular signal-regulated kinase 3 (mitogen-activated protein kinase 6 [MAPK6])-MAPK-activated protein kinase 5 signaling complex regulates septin function and dendrite morphology. *Mol. Cell. Biol., 32*, 2467-78. ↗

Editions

2015-05-12	Reviewed	Mathien, S.
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2015-05-13	Edited	Rothfels, K.

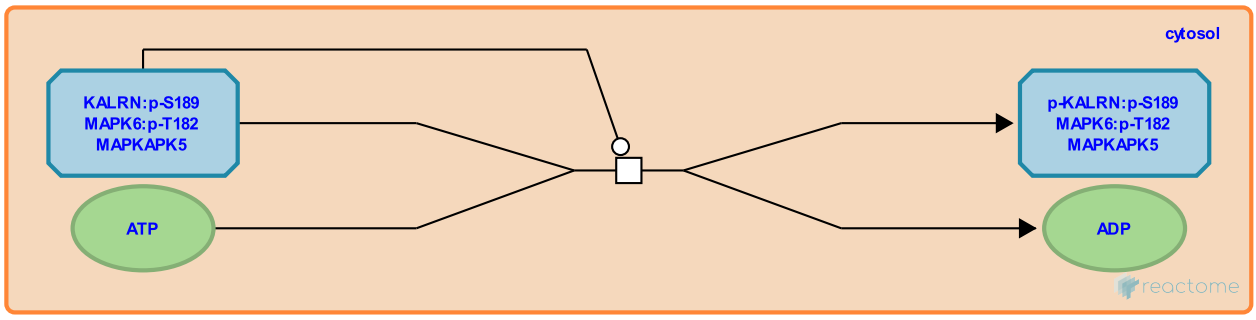
MAPKAPK5 phosphorylates KALRN ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692768

Type: transition

Compartments: cytosol



KALRN is phosphorylated in a MAPKAPK5-dependent manner (Brand et al, 2012).

Literature references

Schumacher, S., Brand, F., Kant, S., Meloche, S., Kotlyarov, A., Gaestel, M. et al. (2012). The extracellular signal-regulated kinase 3 (mitogen-activated protein kinase 6 [MAPK6])-MAPK-activated protein kinase 5 signaling complex regulates septin function and dendrite morphology. *Mol. Cell. Biol., 32*, 2467-78. ↗

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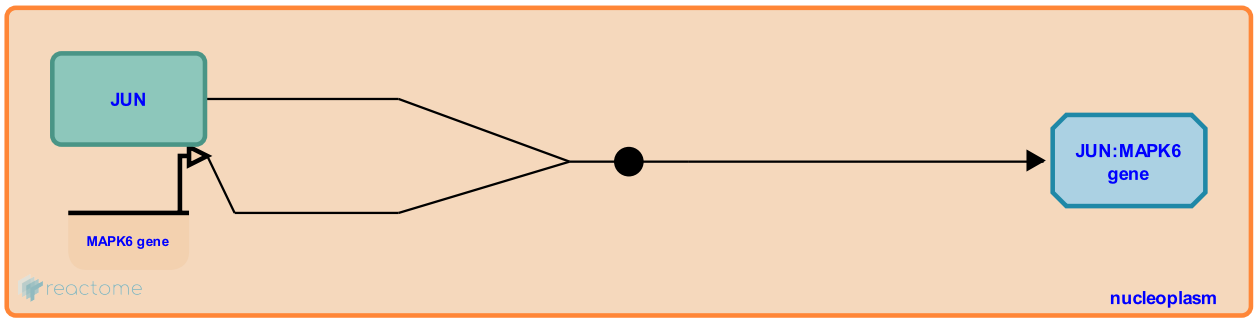
JUN binds MAPK6 gene ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692761

Type: binding

Compartments: nucleoplasm



MAPK6 expression is stimulated in response to cytokines through JUN-mediated transcriptional activation. Phosphorylated JUN binds to a canonical JUN-binding site in the MAPK6 gene as assessed by ChIP, and stimulates transcription in response to TNFalpha (Wang et al, 2014).

Literature references

O'Malley, BW., Wu, RC., Bian, K., Vallabhaneni, S., Long, W., Zhang, B. et al. (2014). ERK3 promotes endothelial cell functions by upregulating SRC-3/SP1-mediated VEGFR2 expression. *J. Cell. Physiol., 229,* 1529-37. ↗

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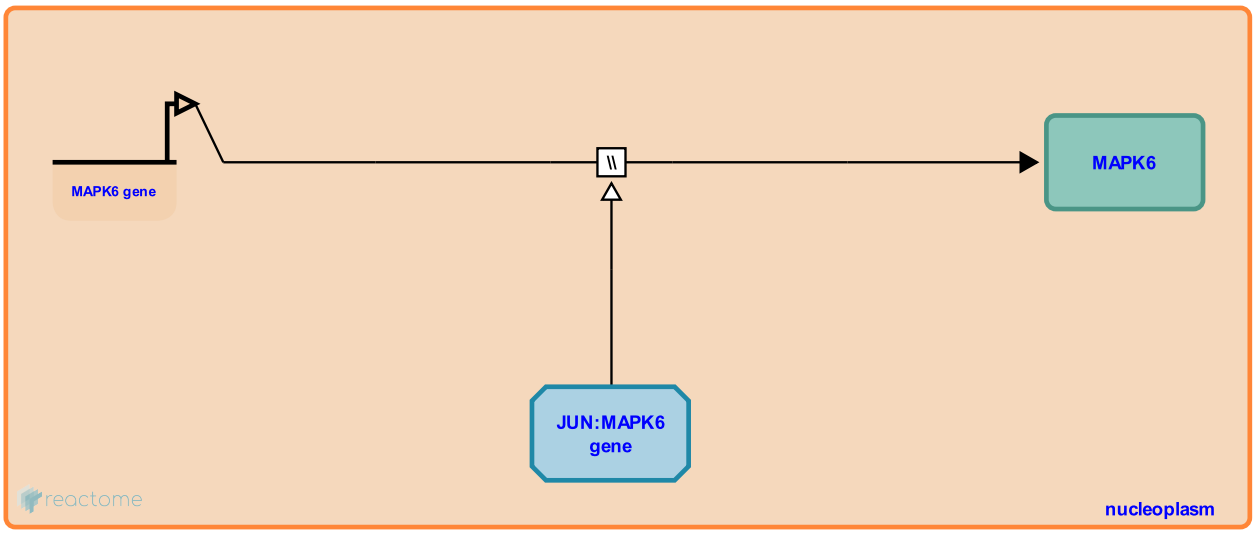
JUN positively regulates MAPK6 gene expression ↗

Location: MAPK6/MAPK4 signaling

Stable identifier: R-HSA-5692788

Type: omitted

Compartments: nucleoplasm



Binding of JUN to its target sequence activates expression of MAPK6 (Wang et al, 2014).

Literature references

O'Malley, BW., Wu, RC., Bian, K., Vallabhaneni, S., Long, W., Zhang, B. et al. (2014). ERK3 promotes endothelial cell functions by upregulating SRC-3/SP1-mediated VEGFR2 expression. *J. Cell. Physiol., 229*, 1529-37. ↗

Editions

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