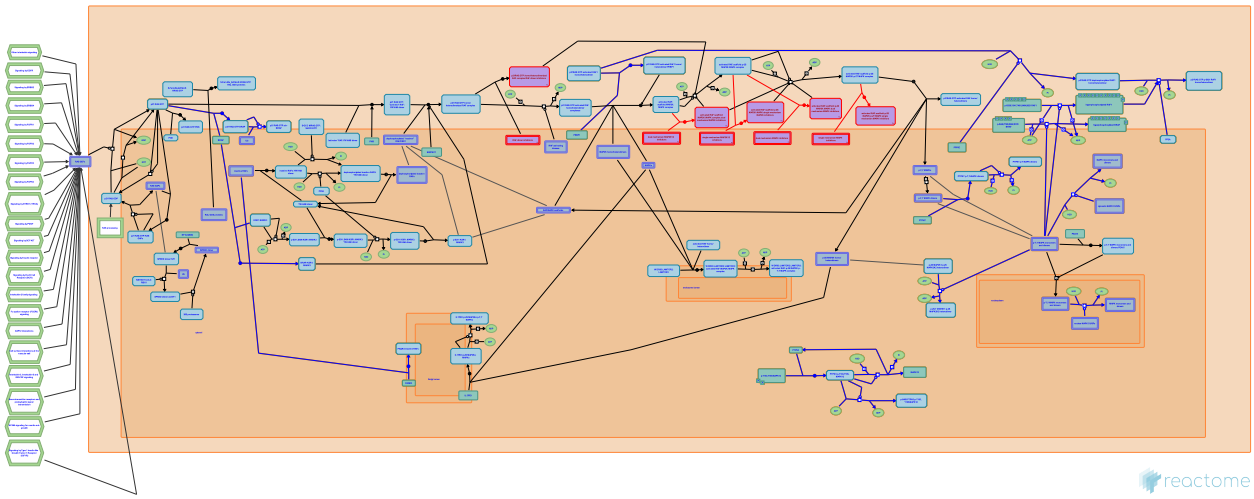
Negative regulation of MAPK pathway



Gavathiotis, E., Orlic-Milacic, M., Roskoski, R Jr., Rothfels, K.

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28/04/2024

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. ↗

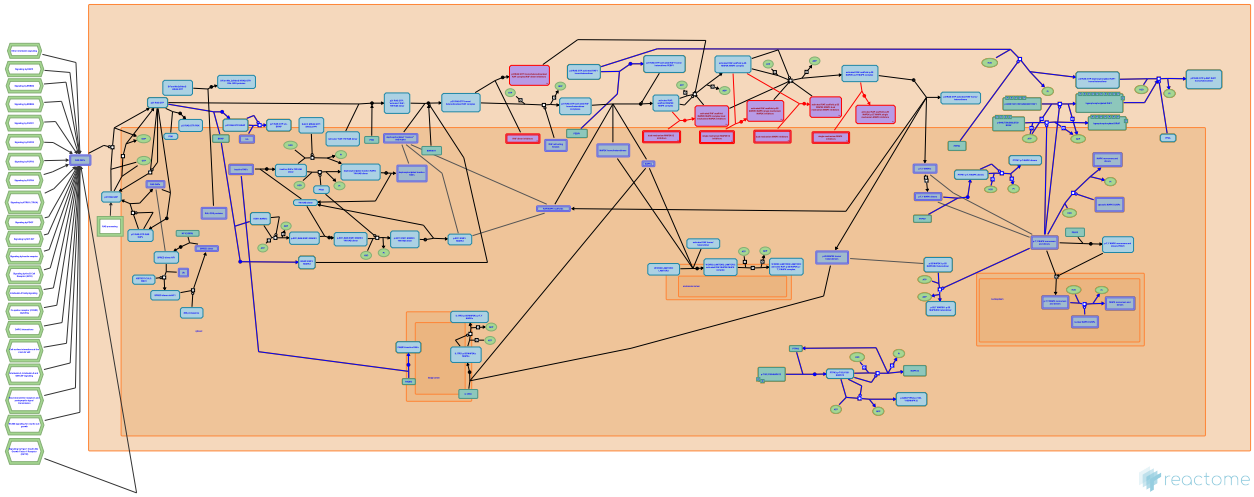
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Negative regulation of MAPK pathway ↗

Stable identifier: R-HSA-5675221



The duration and extent of activated MAPK signaling is regulated at many levels through mechanisms that include phosphorylation and dephosphorylation, changes to protein interacting partners and subcellular localization (reviewed in Matallanas et al, 2011).

Activated RAF proteins are subject to MAPK-dependent phosphorylation that promotes the subsequent dephosphorylation of the activation loop and NtA region, terminating RAF kinase activity. This dephosphorylation, catalyzed by PP2A and PP5, primes the RAF proteins for PKA or AKT-mediated phosphorylation of residues S259 and S621, restoring the 14-3-3 binding sites and returning the RAF proteins to the inactive state (von Kriegsheim et al, 2006; Dougherty et al, 2005; reviewed in Matallanas et al, 2011). The phosphorylated RAF1 NtA is also subject to additional regulation through binding to the PEBP1 protein, which promotes its dissociation from MAP2K substrates (Shin et al, 2009).

Activated MAPK proteins also phosphorylate T292 of MAP2K1; this phosphorylation limits the activity of MAP2K1, and indirectly affects MAP2K2 activity through by modulating the activity of the MAP2K heterodimer (Catalanotti et al, 2009; reviewed in Matallanas et al, 2011).

Dephosphorylation of MAPKs by the dual specificity MAPK phosphatases (DUSPs) plays a key role in limiting the extent of pathway activation (Owens et al, 2007; reviewed in Roskoski, 2012b). Class I DUSPs are localized in the nucleus and are induced by activation of the MAPK pathway, establishing a negative feedback loop, while class II DUSPs dephosphorylate cytoplasmic MAPKs (reviewed in Rososki, 2012b).
MAPK signaling is also regulated by the RAS GAP-mediated stimulation of intrinsic RAS GTPase activity which returns RAS to the inactive, GDP bound state (reviewed in King et al, 2013).

Literature references

Romano, D., Matallanas, D., Rauch, J., Zebisch, A., Birtwistle, M., Kolch, W. et al. (2011). Raf family kinases: old dogs have learned new tricks. *Genes Cancer, 2*, 232-60. ↗

Keyse, SM., Owens, DM. (2007). Differential regulation of MAP kinase signalling by dual-specificity protein phosphatases. *Oncogene, 26*, 3203-13. ↗

Fee, F., Shin, SY., McFerran, B., Cho, KH., Kolch, W., Choo, SM. et al. (2009). Positive- and negative-feedback regulations coordinate the dynamic behavior of the Ras-Raf-MEK-ERK signal transduction pathway. *J. Cell. Sci., 122*, 425-35. ↗

Grindlay, GJ., Dhillon, AS., Kolch, W., Pitt, A., von Kriegsheim, A. (2006). Regulation of the Raf-MEK-ERK pathway by protein phosphatase 5. *Nat. Cell Biol., 8*, 1011-6. ↗

Jesenberger, V., de Matos Simoes, R., Galabova-Kovacs, G., Baccarini, M., Reyes, G., Carugo, O. et al. (2009). A Mek1-Mek2 heterodimer determines the strength and duration of the Erk signal. *Nat. Struct. Mol. Biol., 16*, 294-303. ↗

Editions

2015-02-12	Authored, Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

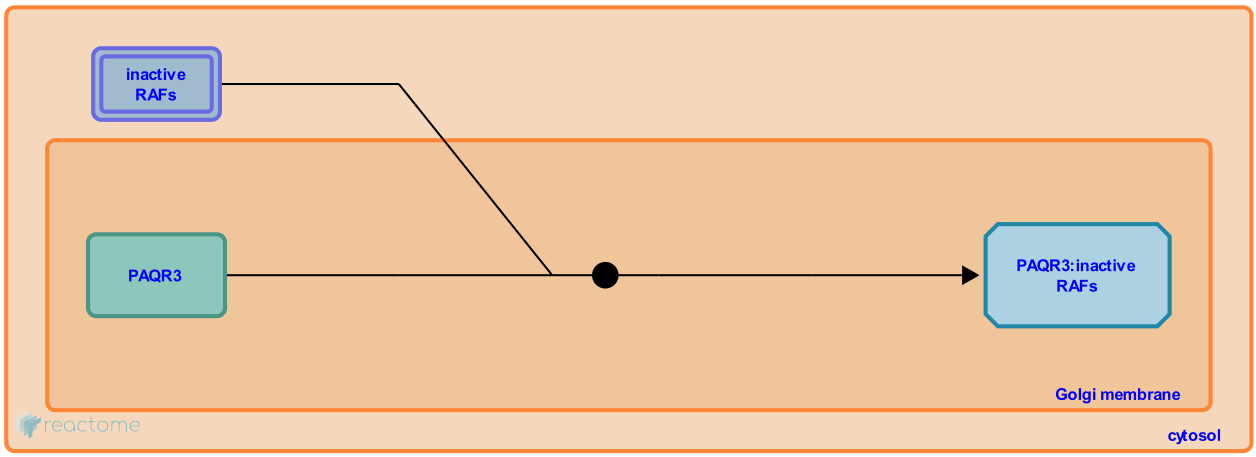
PAQR3 binds inactive RAFs ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5674140

Type: binding

Compartments: Golgi membrane



PAQR3, also known as RKTG (Raf kinase trapping to Golgi) is a multi-pass transmembrane protein that binds to RAF1 and BRAF and sequesters them in the Golgi. This inhibits the interaction of RAF with activated RAS and the plasma membrane and inhibits RAF signaling (Feng et al, 2007; Fan et al, 2008; Luo et al, 2008).

Literature references

Chen, Y., Jiang, X., He, J., Zhang, Y., Wang, Z., Fan, F. et al. (2008). RKTG sequesters B-Raf to the Golgi apparatus and inhibits the proliferation and tumorigenicity of human malignant melanoma cells. *Carcinogenesis, 29*, 1157-63. ↗

Luo, X., Chen, Y., He, J., Wang, Z., Fan, F., Feng, L. et al. (2007). Spatial regulation of Raf kinase signaling by RKTG. *Proc. Natl. Acad. Sci. U.S.A., 104*, 14348-53. ↗

Luo, X., Feng, GS., Chen, Y., Jiang, X., Wang, Z., Xiao, F. et al. (2008). Characterization of the topology and functional domains of RKTG. *Biochem. J., 414*, 399-406. ↗

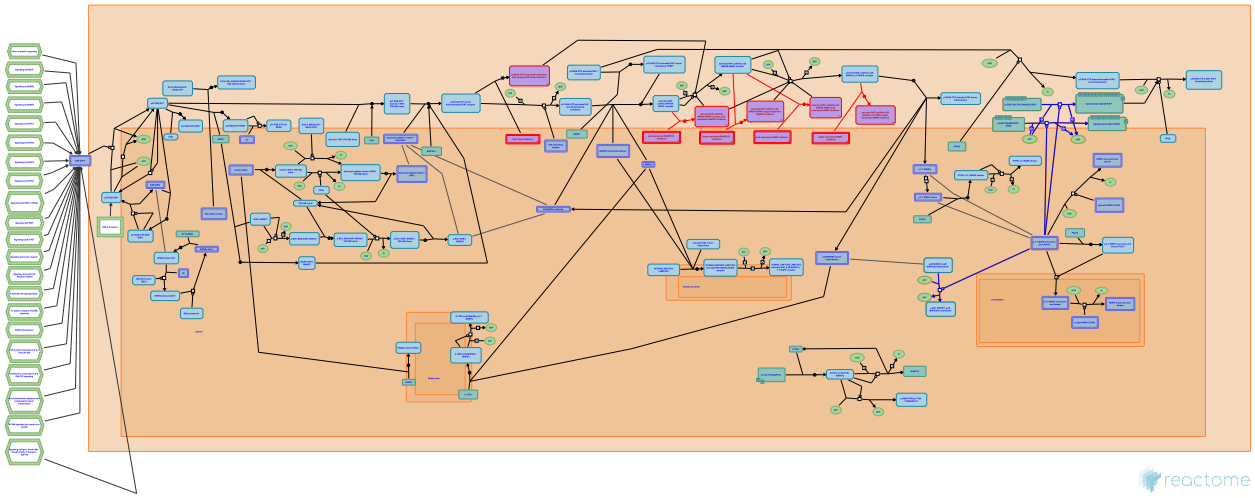
Editions

2015-02-11	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

Negative feedback regulation of MAPK pathway ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5674499



MAPK pathway activation is limited by a number of negative feedback loops established by MAPK-dependent phosphorylations. Known substrates of activated MAPK proteins that lie upstream in the RAF/MAPK pathway include SOS, RAF1, BRAF, and MAP2K1 (Buday et al, 1995; Dong et al, 1996; Dougherty et al, 2005; Sturm et al, 2010; Fritsche-Guenther et al, 2011; Rushworth et al, 2006; Brummer et al, 2003; Ritt et al, 2010; Catalanotti et al, 2009)

Literature references

Specht, SI., Monson, DM., Morrison, DK., Ritt, DA. (2010). Impact of feedback phosphorylation and Raf heterodimerization on normal and mutant B-Raf signaling. *Mol. Cell. Biol., 30*, 806-19. ↗

Herr, R., Sieber, A., Sers, C., Fritsche-Guenther, R., Brummer, T., Braun, S. et al. (2011). Strong negative feedback from Erk to Raf confers robustness to MAPK signalling. *Mol. Syst. Biol., 7*, 489. ↗

Calder, M., Sturm, OE., Vyshemirsky, V., Orton, R., Kholodenko, B., Gilbert, D. et al. (2010). The mammalian MAPK/ERK pathway exhibits properties of a negative feedback amplifier. *Sci Signal, 3*, ra90. ↗

Brummer, T., Naegele, H., Misawa, Y., Reth, M. (2003). Identification of novel ERK-mediated feedback phosphorylation sites at the C-terminus of B-Raf. *Oncogene, 22*, 8823-34. ↗

Warne, PH., Buday, L., Downward, J. (1995). Downregulation of the Ras activation pathway by MAP kinase phosphorylation of Sos. *Oncogene, 11*, 1327-31. ↗

Editions

2015-02-12	Authored, Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

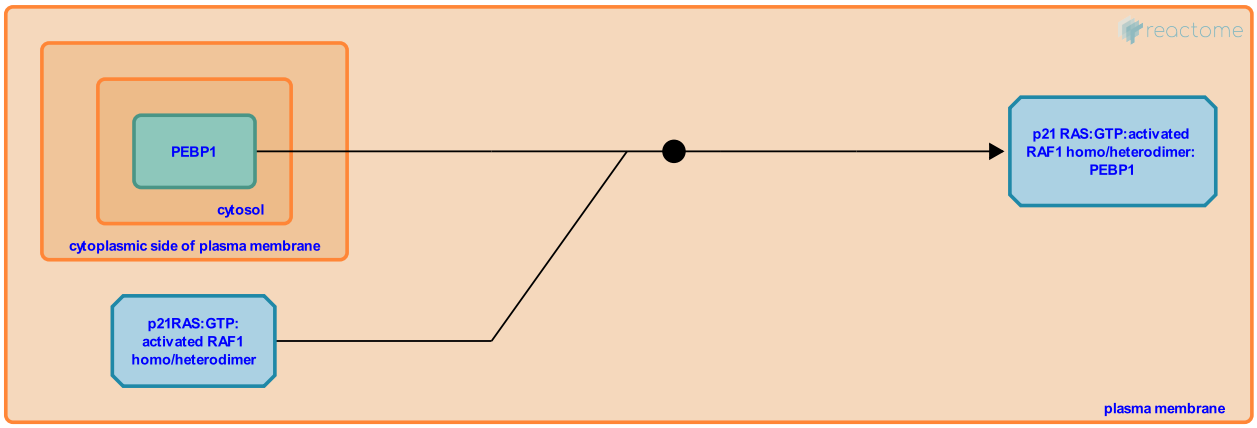
PEBP1 binds activated RAF1 ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5675417

Type: binding

Compartments: plasma membrane



PEBP1, also known as RKIP (Raf kinase inhibitor protein), is a negative regulator of RAF1 that binds to the phosphorylated NtA region and prevents activation of MAP2K substrates (Yeung et al, 1999; Yeung et al, 2000; Rath et al, 2008; Park et al, 2006; reviewed in Lorenz et al, 2014). Relief of this PEBP1 repression of RAF1 activity is stimulated by phosphorylation of PEBP1, which promotes it dissociation from RAF1. Candidate kinases for phosphorylation of PEBP1 include PKC and the MAPKs themselves, which would establish a positive feedback loop stimulating MAPK pathway activity (Corbit et al, 2003; Cho et al, 2003; Shin et al, 2009).

Literature references

Yeung, KC., Beach, S., Park, S., Luo, Z., Kelly, SM., Kolch, W. et al. (2006). Regulation of RKIP binding to the N-region of the Raf-1 kinase. *FEBS Lett., 580*, 6405-12. ↗

Lorenz, K., Deiss, K., Schmid, E. (2014). RKIP: a governor of intracellular signaling. *Crit Rev Oncog, 19*, 489-96. ↗

Yeung, K., Sedivy, JM., Janosch, P., McFerran, B., Kolch, W., Mischak, H. et al. (2000). Mechanism of suppression of the Raf/MEK/extracellular signal-regulated kinase pathway by the raf kinase inhibitor protein. *Mol. Cell. Biol., 20*, 3079-85. ↗

Yeung, KC., Banfield, MJ., Brady, RL., Dignam, JD., Sedivy, JM., Lee, YC. et al. (2008). The RKIP (Raf-1 Kinase Inhibitor Protein) conserved pocket binds to the phosphorylated N-region of Raf-1 and inhibits the Raf-1-mediated activated phosphorylation of MEK. *Cell. Signal., 20*, 935-41. ↗

Fee, F., Shin, SY., McFerran, B., Cho, KH., Kolch, W., Choo, SM. et al. (2009). Positive- and negative-feedback regulations coordinate the dynamic behavior of the Ras-Raf-MEK-ERK signal transduction pathway. *J. Cell. Sci., 122*, 425-35. ↗

Editions

2015-02-16	Authored, Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

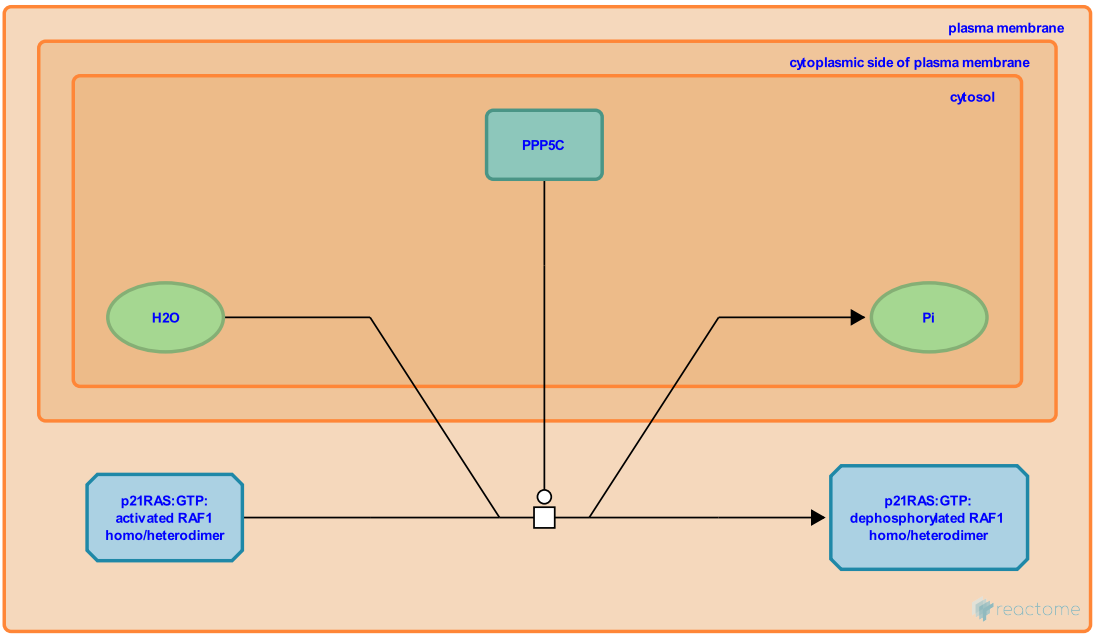
PP5 dephosphorylates RAF1 S338 ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5675433

Type: transition

Compartments: plasma membrane



PPP5C dephosphorylates S338 in the NtA region of RAF1, which reduces the catalytic activity of RAF1 towards MAP2K proteins (von Kriegsheim et al, 2006; reviewed in Matallanas et al, 2011).

Followed by: PP2A dephosphorylates RAF1

Literature references

Grindlay, GJ., Dhillon, AS., Kolch, W., Pitt, A., von Kriegsheim, A. (2006). Regulation of the Raf-MEK-ERK pathway by protein phosphatase 5. *Nat. Cell Biol., 8*, 1011-6. ↗

Romano, D., Matallanas, D., Rauch, J., Zebisch, A., Birtwistle, M., Kolch, W. et al. (2011). Raf family kinases: old dogs have learned new tricks. *Genes Cancer, 2*, 232-60. ↗

Editions

2015-02-16	Authored, Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

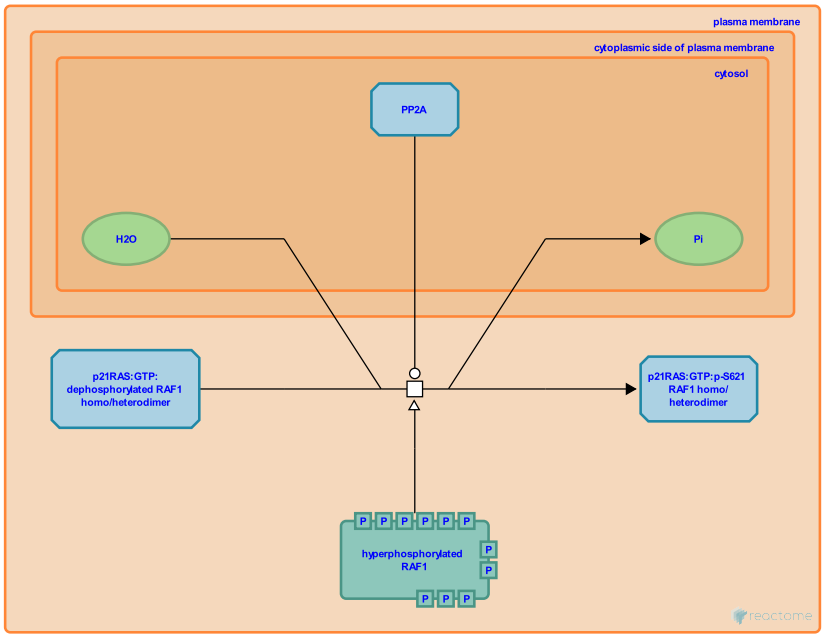
PP2A dephosphorylates RAF1 ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5675431

Type: transition

Compartments: plasma membrane



Along with PPP5C-mediated dephophosphorylation of the NtA region, PP2A contributes to the inactivation of RAF1 by mediating the dephosphorylation of AL loop residues. PP2A-mediated dephosphorylation of RAF1 may be stimulated by the prior hyperphosphorylation of RAF1 by MAPKs (Dougherty et al, 2005; reviewed in Matallanas et al, 2011).

Preceded by: PP5 dephosphorylates RAF1 S338

Literature references

Zhou, XZ., Veenstra, TD., Dougherty, MK., Lu, KP., Müller, J., Copeland, TD. et al. (2005). Regulation of Raf-1 by direct feedback phosphorylation. *Mol. Cell, 17*, 215-24. ↗

Romano, D., Matallanas, D., Rauch, J., Zebisch, A., Birtwistle, M., Kolch, W. et al. (2011). Raf family kinases: old dogs have learned new tricks. *Genes Cancer, 2*, 232-60. ↗

Editions

2015-02-16	Authored, Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

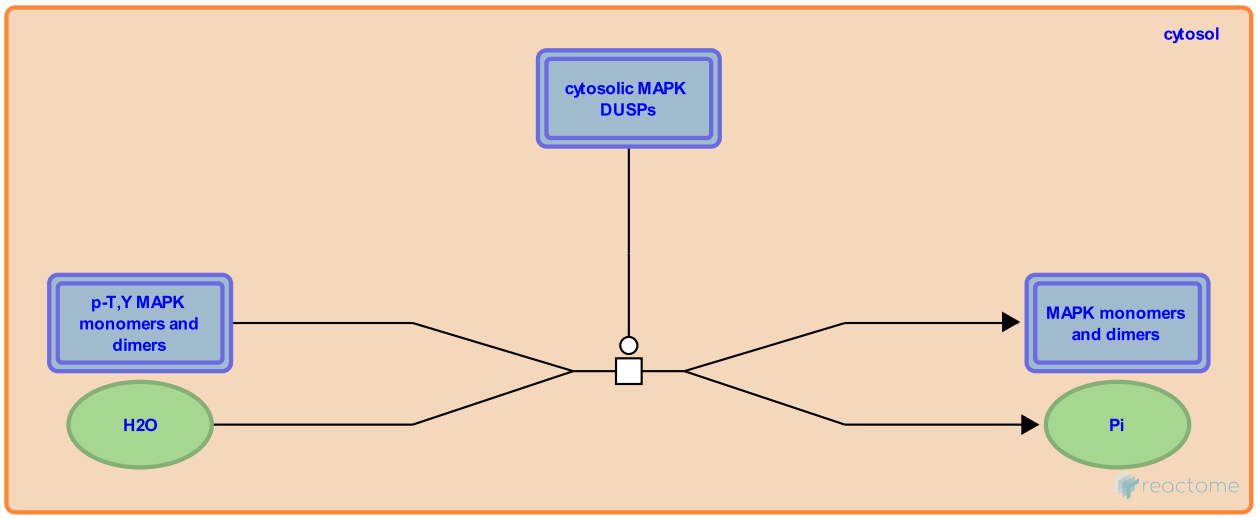
Cytosolic DUSPs dephosphorylate MAPKs ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5675376

Type: transition

Compartments: cytosol



MAPKs are inactivated by dephosphorylation of the activation loop T and Y residues by dual-specificity MAPK phosphatases (DUSPs) (reviewed in Roskoski, 2012b). Cytosolic MAPKs are dephosphorylated by the MAPK-specific class II DUSPs 6,7 and 9, but may also be dephosphorylated by cytosolic forms of class III DUSPs 8, 10 and 16, which preferentially dephosphorylate p38 and JNK MAP kinases (reviewed in Bermudez et al, 2010; Kandoh and Nishida, 2007).

Literature references

Kondoh, K., Nishida, E. (2007). Regulation of MAP kinases by MAP kinase phosphatases. *Biochim. Biophys. Acta, 1773*, 1227-37. ↗

Gimond, C., Pagès, G., Bermudez, O. (2010). The dual-specificity MAP kinase phosphatases: critical roles in development and cancer. *Am. J. Physiol., Cell Physiol., 299*, C189-202. ↗

Roskoski, R Jr. (2012). ERK1/2 MAP kinases: structure, function, and regulation. *Pharmacol. Res., 66*, 105-43. ↗

Editions

2015-02-15	Authored, Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

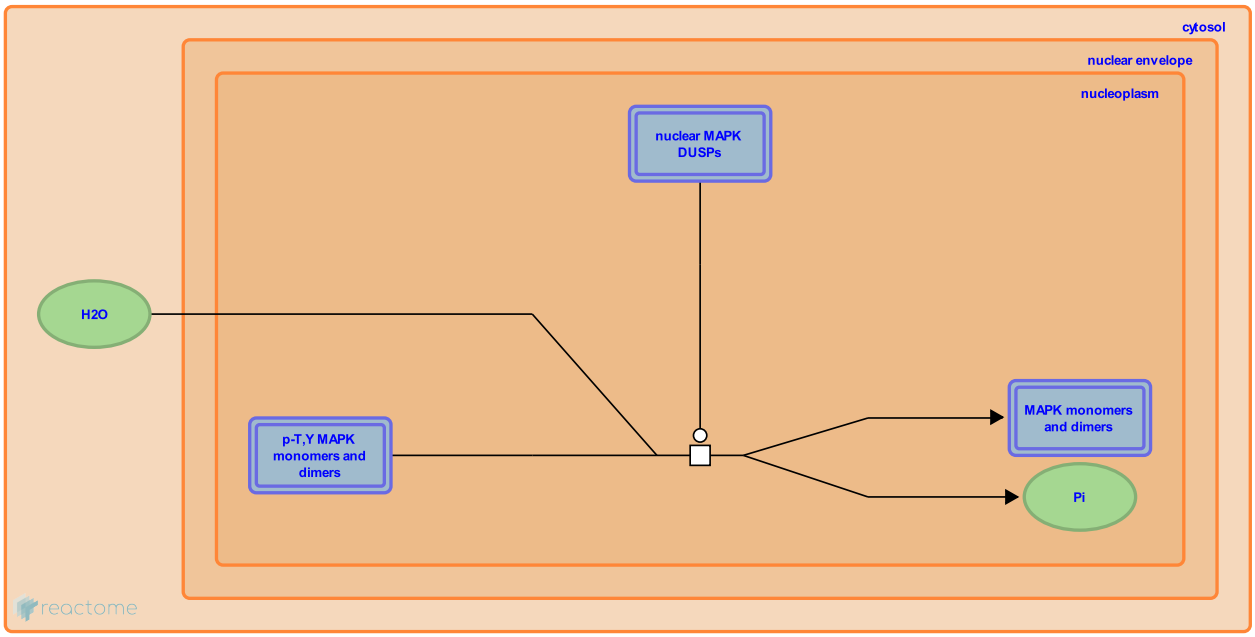
Nuclear DUSPs dephosphorylate MAPKs ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5675373

Type: transition

Compartments: nucleoplasm



MAPKs are inactivated by dephosphorylation of the activation loop T and Y residues by dual-specificity MAPK phosphatases (DUSPs) (reviewed in Roskoski, 2012b). Class 1 DUSPs, including DUSP 1, 2, 4 and 5 are nuclear and are generally activated by the same extracellular stimuli that promote MAPK signaling, establishing a negative feedback loop. DUSP5 is specific for MAPK3 and 1, while the other class 1 enzymes have broad specificity. Nuclear MAPKs may also be inactivated by nuclear forms of class III DUSPs, including DUSP8, 10 and 16, although the preferred substrate of these enzymes are the p38 and JNK MAP kinases (reviewed in Bermudez et al, 2010; Kondoh and Nishida, 2007).

Literature references

Kondoh, K., Nishida, E. (2007). Regulation of MAP kinases by MAP kinase phosphatases. *Biochim. Biophys. Acta, 1773*, 1227-37. ↗

Gimond, C., Pagès, G., Bermudez, O. (2010). The dual-specificity MAP kinase phosphatases: critical roles in development and cancer. *Am. J. Physiol., Cell Physiol., 299*, C189-202. ↗

Roskoski, R Jr. (2012). ERK1/2 MAP kinases: structure, function, and regulation. *Pharmacol. Res., 66*, 105-43. ↗

Editions

2015-02-15	Authored, Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

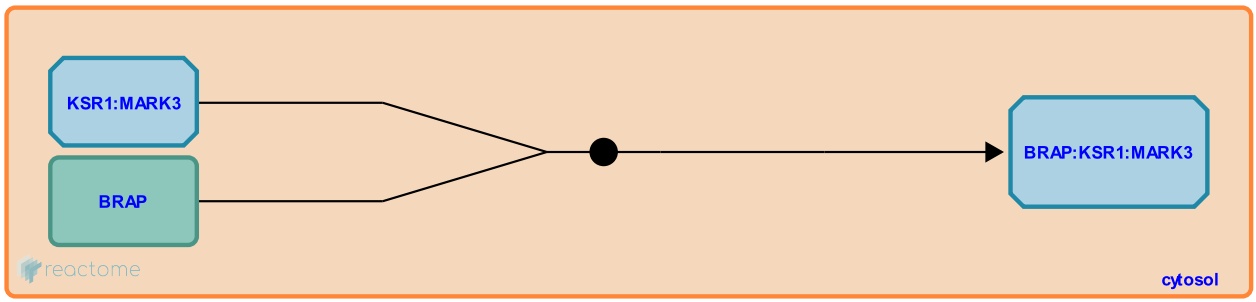
BRAP binds KSR1:MARK3 ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5674019

Type: binding

Compartments: cytosol



BRAP is a negative regulator of MAPK signaling that binds KSR1 as assessed by coimmunoprecipitation. This interaction abrogates KSR1 homodimer and KSR1:RAF heterodimer formation, and disrupts the recruitment of MAP2K kinases to RAF (Methany et al, 2004; Chen et al, 2008; reviewed in Methany et al, 2009). BRAP inhibition of KSR1 is relieved in an unknown manner by autoubiquitination after RAS pathway activation (reviewed in Methany et al, 2009).

Literature references

White, MA., Kortum, RL., Lewis, RE., Razidlo, GL., Matheny, SA., Chen, C. (2004). Ras regulates assembly of mitogenic signalling complexes through the effector protein IMP. *Nature, 427*, 256-60. ↗

White, MA., Lewis, RE., Chen, C. (2008). IMP modulates KSR1-dependent multivalent complex formation to specify ERK1/2 pathway activation and response thresholds. *J. Biol. Chem., 283*, 12789-96. ↗

White, MA., Matheny, SA. (2009). Signaling threshold regulation by the Ras effector IMP. *J. Biol. Chem., 284*, 11007-11 . ↗

Editions

2015-02-06	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

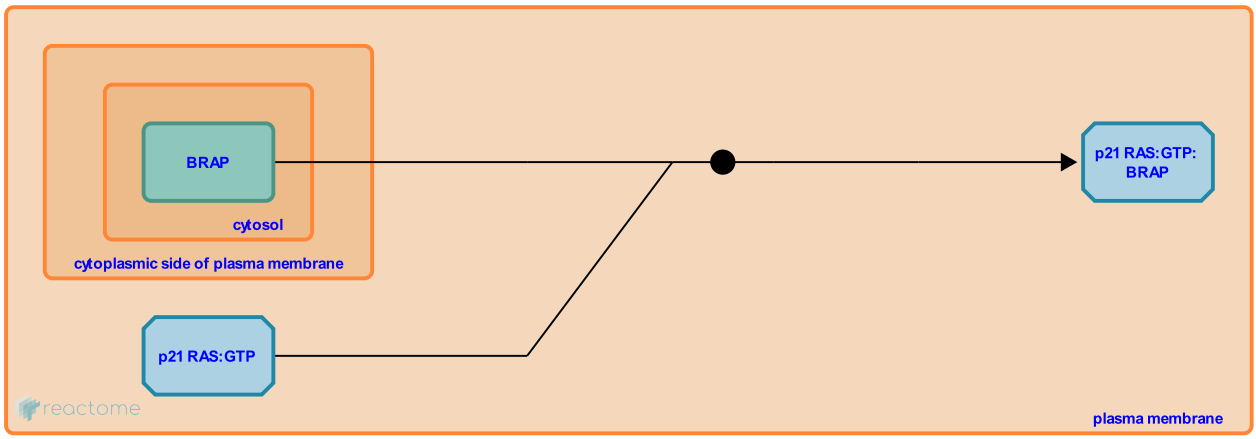
BRAP binds RAS:GTP ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5674018

Type: binding

Compartments: plasma membrane



BRAP is a negative regulator of the RAF/MAPK cascade that inhibits the homo- and heterodimerization of KSR1 and RAF and preventing downstream signal propagation (Matheny et al, 2004; Chen et al, 2008; reviewed in Matheny et al, 2009). Upon RAS stimulation, BRAP binds to RAS:GTP. This stimulates BRAP's E3 HECT ubiquitin ligase activity, promoting its autoubiquitination and thereby relieving the inhibition of KSR1 activity (Matheny et al, 2004; reviewed in Matheny et al, 2009). USP15 is a deubiquitinase that stabilizes BRAP protein levels and thus acts to dampen MAPK signaling (Hayes et al, 2013).

Followed by: BRAP autoubiquitinates

Literature references

White, MA., Kortum, RL., Lewis, RE., Razidlo, GL., Matheny, SA., Chen, C. (2004). Ras regulates assembly of mitogenic signalling complexes through the effector protein IMP. *Nature, 427*, 256-60. ↗

White, MA., Lewis, RE., Chen, C. (2008). IMP modulates KSR1-dependent multivalent complex formation to specify ERK1/2 pathway activation and response thresholds. *J. Biol. Chem., 283*, 12789-96. ↗

White, MA., Matheny, SA. (2009). Signaling threshold regulation by the Ras effector IMP. *J. Biol. Chem., 284*, 11007-11 . ↗

Clague, MJ., Coulson, JM., MacDonald, E., Sanderson, CM., Urbé, S., Liu, H. et al. (2012). Direct and indirect control of mitogen-activated protein kinase pathway-associated components, BRAP/IMP E3 ubiquitin ligase and CRAF/RAF1 kinase, by the deubiquitylating enzyme USP15. *J. Biol. Chem., 287*, 43007-18. ↗

Editions

2015-02-06	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

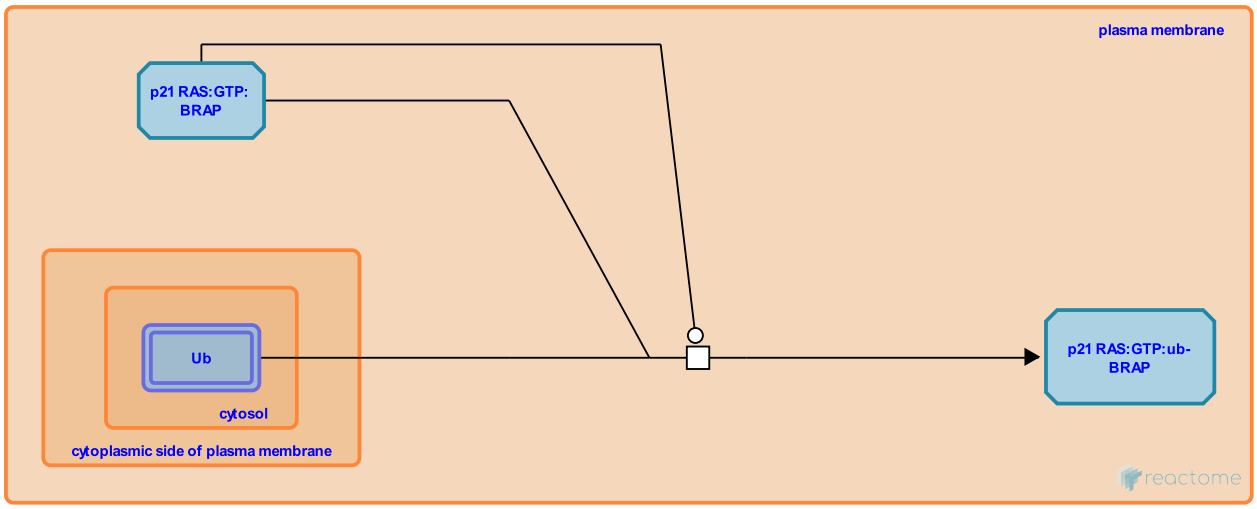
BRAP autoubiquitinates ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-5674022

Type: transition

Compartments: plasma membrane



Binding to activated RAS stimulates the ubiquitinase activity of BRAP, promoting autoubiquitination and relieving the inhibition of KSR1 (Methany et al, 2004; Chen et al, 2008; Methany et al, 2009).

Preceded by: BRAP binds RAS:GTP

Literature references

White, MA., Kortum, RL., Lewis, RE., Razidlo, GL., Matheny, SA., Chen, C. (2004). Ras regulates assembly of mitogenic signalling complexes through the effector protein IMP. *Nature, 427*, 256-60. ↗

White, MA., Lewis, RE., Chen, C. (2008). IMP modulates KSR1-dependent multivalent complex formation to specify ERK1/2 pathway activation and response thresholds. *J. Biol. Chem., 283*, 12789-96. ↗

White, MA., Matheny, SA. (2009). Signaling threshold regulation by the Ras effector IMP. *J. Biol. Chem., 284*, 11007-11 . ↗

Editions

2015-02-06	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

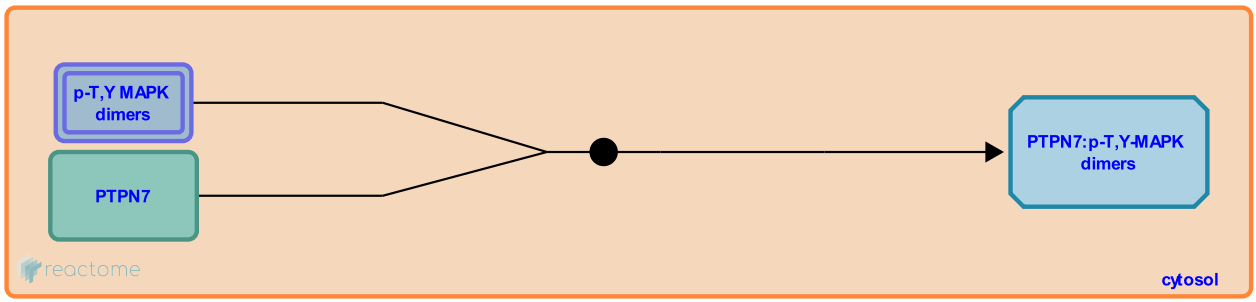
PTPN7 binds p-T,Y-MAPK ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-9635743

Type: binding

Compartments: cytosol



PTPN7 (HePTP) protein tyrosine phosphatase binds to MAPK1 (ERK2) (Saxena et al. 1999, Munoz et al. 2003) and MAPK3 (ERK1) (Oh-hora et al. 1999, Munoz et al. 2003). The interaction of PTPN7 with MAPKs involves the KIM (kinase-interaction motif) of PTPN7.
PTPN7 may have a preference for ERK2 over ERK1 (Pettiford and Herbst 2000). ERK1 used in the study by Oh-hora et al. 1999 was likely human, but it is not certain. In the study by Munoz et al. 2003, interaction of PTPN7 with rat ERK1 was demonstrated, but the origin of PTPN7 was not specified.

Followed by: PTPN7 dephosphorylates p-T,Y-MAPKs

Literature references

Pettiford, SM., Herbst, R. (2000). The MAP-kinase ERK2 is a specific substrate of the protein tyrosine phosphatase HePTP. *Oncogene, 19*, 858-69. ↗

Kosugi, A., Oh-hora, M., Adachi, M., Imai, K., Mori, Y., Hamaoka, T. et al. (1999). Direct suppression of TCR-mediated activation of extracellular signal-regulated kinase by leukocyte protein tyrosine phosphatase, a tyrosine-specific phosphatase. *J. Immunol., 163*, 1282-8. ↗

Muñoz, JJ., Tárrega, C., Pulido, R., Blanco-Aparicio, C. (2003). Differential interaction of the tyrosine phosphatases PTP-SL, STEP and HePTP with the mitogen-activated protein kinases ERK1/2 and p38alpha is determined by a kinase specificity sequence and influenced by reducing agents. *Biochem. J., 372*, 193-201. ↗

Brockdorff, J., Williams, S., Mustelin, T., Saxena, M., Gilman, J. (1999). Inhibition of T cell signaling by mitogen-activated protein kinase-targeted hematopoietic tyrosine phosphatase (HePTP). *J. Biol. Chem., 274*, 11693-700. ↗

Editions

2019-09-23	Authored	Orlic-Milacic, M.
2019-10-28	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

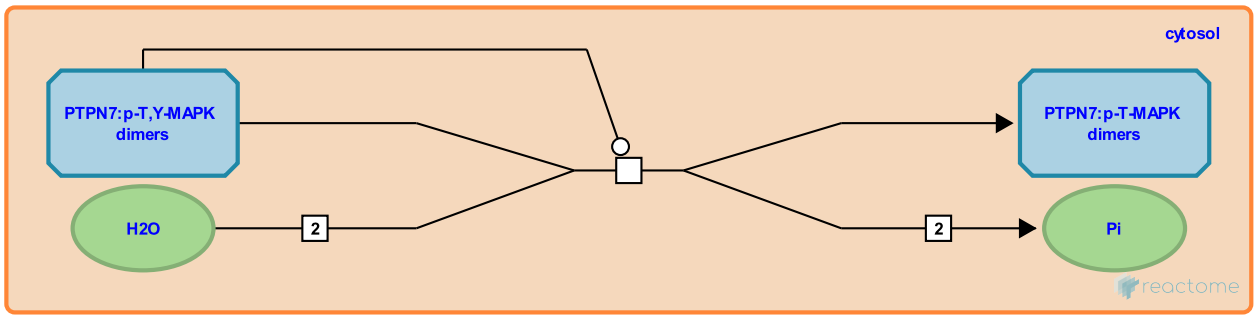
PTPN7 dephosphorylates p-T,Y-MAPKs ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-9635739

Type: transition

Compartments: cytosol



Protein tyrosine phosphatase PTPN7 (also known as HePTP) dephosphorylates tyrosine residues of MAPK1 (ERK2) (Saxena et al. 1999, Pettiford and Herbst 2000) and MAPK3 (ERK1) (Saxena et al. 1999), leading to reduction in their catalytic activity.

Preceded by: PTPN7 binds p-T,Y-MAPK

Literature references

Pettiford, SM., Herbst, R. (2000). The MAP-kinase ERK2 is a specific substrate of the protein tyrosine phosphatase HePTP. *Oncogene, 19*, 858-69. ↗

Brockdorff, J., Williams, S., Mustelin, T., Saxena, M., Gilman, J. (1999). Inhibition of T cell signaling by mitogen-activated protein kinase-targeted hematopoietic tyrosine phosphatase (HePTP). *J. Biol. Chem., 274*, 11693-700. ↗

Editions

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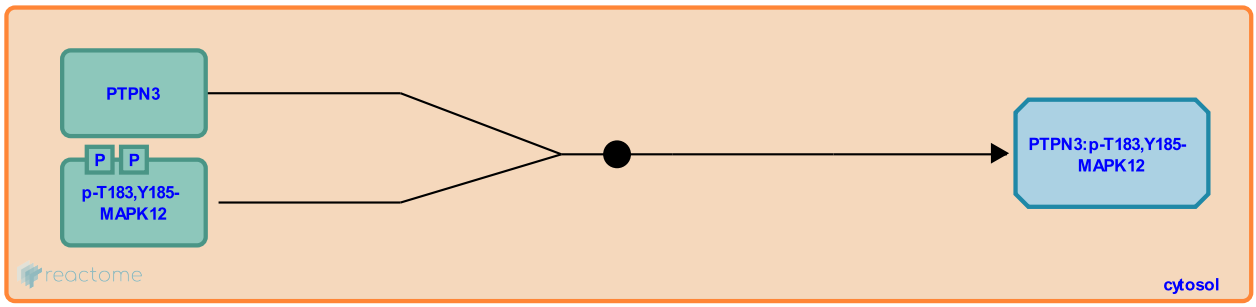
PTPN3 binds p-T183,Y185 MAPK12 ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-8867654

Type: binding

Compartments: cytosol



PTPN3 is a protein phosphatase that dephosphorylates MAPK12, also known as p38 gamma. Phosphorylation of the p38 family of MAPK is associated with suppression of RAS signaling, and consistent with this, binding and dephosphorylation of MAPK12 by PTPN3 promotes RAS-induced transformation (Tang et al, 2005; Hou et al, 2010; Chen et al, 2014).
Dephosphorylation is promoted by a direct binding between phosphorylated MAPK12 and PTPN3, mediated by an interaction between the PTPN3 PDZ domain and the isoform-specific ETPL domain of MAPK12. Binding of PTPN3 and phosphorylated MAPK12 relieves an autoinhibitory conformation of the phosphatase and promotes MAPK12 dephosphorylation (Hou et al, 2010; Chen et al, 2014). How dephosphorylated MAPK12 promotes RAS signaling remains to be elucidated.

Followed by: PTPN3 dephosphorylates MAPK12

Literature references

Chen, G., Qi, X., Mercola, D., Tang, J., Han, J. (2005). Essential role of p38gamma in K-Ras transformation independent of phosphorylation. *J. Biol. Chem., 280*, 23910-7. ↗

Wang, AH., Chen, KE., Santhanam, A., Meng, TC., Ho, MR., Chou, CC. et al. (2014). Reciprocal allosteric regulation of p38γ and PTPN3 involves a PDZ domain-modulated complex formation. *Sci Signal, 7*, ra98. ↗

Chen, G., Pohl, N., Zhi, HY., Basir, Z., Qi, XM., Li, RS. et al. (2010). PTPH1 dephosphorylates and cooperates with p38gamma MAPK to increase ras oncogenesis through PDZ-mediated interaction. *Cancer Res., 70*, 2901-10. ↗

Editions

2016-03-21	Authored, Edited	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.

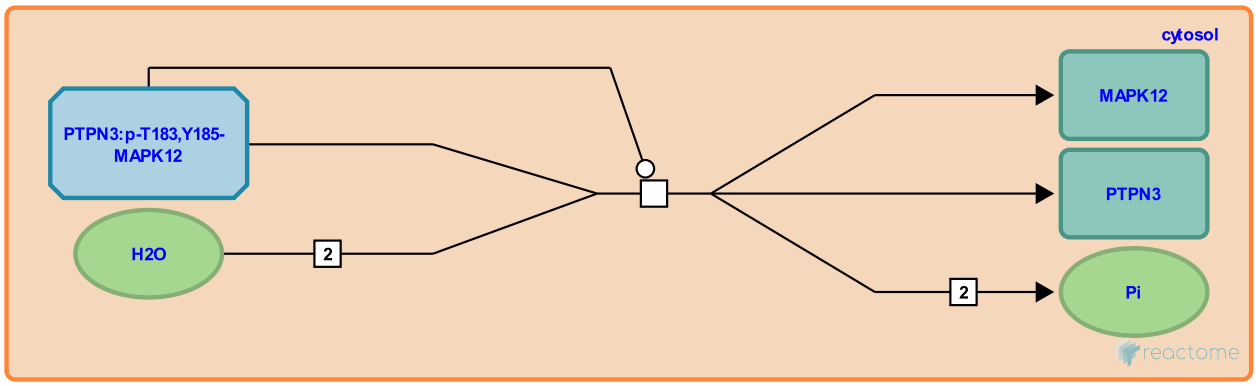
PTPN3 dephosphorylates MAPK12 ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-8867658

Type: transition

Compartments: cytosol



PTPN3-mediated dephosphorylation of MAPK12 promotes RAS signaling and transformation through an unknown mechanism (Tang et al, 2005; Hou et al, 2010; Chen et al, 2014). Consistent with a role for dephosphorylated MAPK12 and PTPN3 in promoting RAS signaling, depletion of PTPN3 or MAPK12 inhibits malignant growth in RAS-activated human cancer cell lines and in mouse models. In addition, RAS signaling increases protein levels of both MAPK12 and PTPN3, suggesting the presence of a positive feedback loop (Hou et al, 2010). Dephosphorylation of MAPK12 may promote its incorporation into complexes with ERK proteins, though the functional significance of this is unclear (Tang et al, 2005).

Preceded by: PTPN3 binds p-T183,Y185 MAPK12

Literature references

Chen, G., Qi, X., Mercola, D., Tang, J., Han, J. (2005). Essential role of p38gamma in K-Ras transformation independent of phosphorylation. *J. Biol. Chem., 280*, 23910-7. ↗

Wang, AH., Chen, KE., Santhanam, A., Meng, TC., Ho, MR., Chou, CC. et al. (2014). Reciprocal allosteric regulation of p38γ and PTPN3 involves a PDZ domain-modulated complex formation. *Sci Signal, 7*, ra98. ↗

Chen, G., Pohl, N., Zhi, HY., Basir, Z., Qi, XM., Li, RS. et al. (2010). PTPH1 dephosphorylates and cooperates with p38gamma MAPK to increase ras oncogenesis through PDZ-mediated interaction. *Cancer Res., 70*, 2901-10. ↗

Editions

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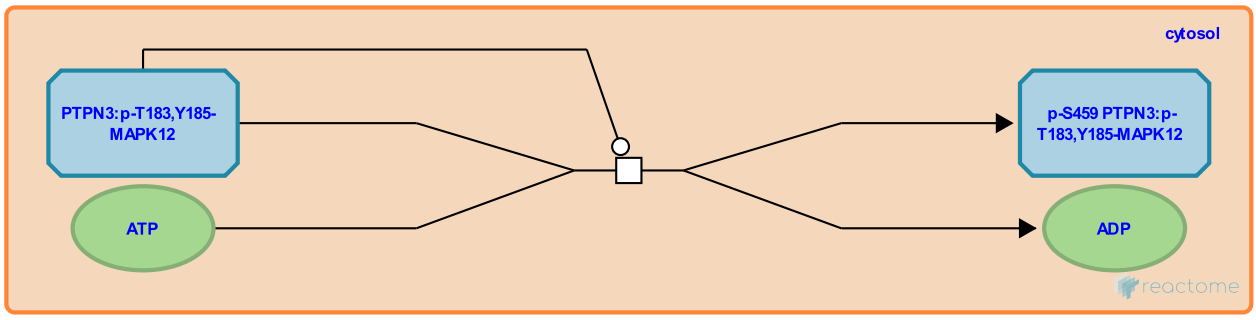
MAPK12 phosphorylates PTPN3 ↗

Location: Negative regulation of MAPK pathway

Stable identifier: R-HSA-8868118

Type: transition

Compartments: cytosol



PTPN3 has been shown to bind to phosphorylated MAPK12 and promote its dephosphorylation, and this interaction is correlated with increased oncogenic signaling through RAS (Hou et al, 2010; Tang et al, 2005; Chen et al, 2014). Although the mechanism for this PTPN3 and MAPK12-dependent activation of RAS signaling is not known, dephosphorylation of MAPK12 allows the recovery of larger amounts of MAPK12 from a complex with ERK proteins, suggesting a possible mechanism. A more recent study, however, has found that PTPN3 is itself phosphorylated in a MAPK12-dependent fashion upon binding with phospho-MAPK12. This phosphorylation antagonizes SOB-induced growth inhibition and increases RAS-dependent oncogenic growth (Hou et al, 2012).

Literature references

Suresh, PS., Chen, G., Mirza, SP., Hou, S., Qi, X., Lepp, A. (2012). p38γ Mitogen-activated protein kinase signals through phosphorylating its phosphatase PTPH1 in regulating ras protein oncogenesis and stress response. *J. Biol. Chem., 287*, 27895-905. ↗

Chen, G., Qi, X., Mercola, D., Tang, J., Han, J. (2005). Essential role of p38gamma in K-Ras transformation independent of phosphorylation. *J. Biol. Chem., 280*, 23910-7. ↗

Wang, AH., Chen, KE., Santhanam, A., Meng, TC., Ho, MR., Chou, CC. et al. (2014). Reciprocal allosteric regulation of p38γ and PTPN3 involves a PDZ domain-modulated complex formation. *Sci Signal, 7*, ra98. ↗

Chen, G., Pohl, N., Zhi, HY., Basir, Z., Qi, XM., Li, RS. et al. (2010). PTPH1 dephosphorylates and cooperates with p38gamma MAPK to increase ras oncogenesis through PDZ-mediated interaction. *Cancer Res., 70*, 2901-10. ↗

Editions

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