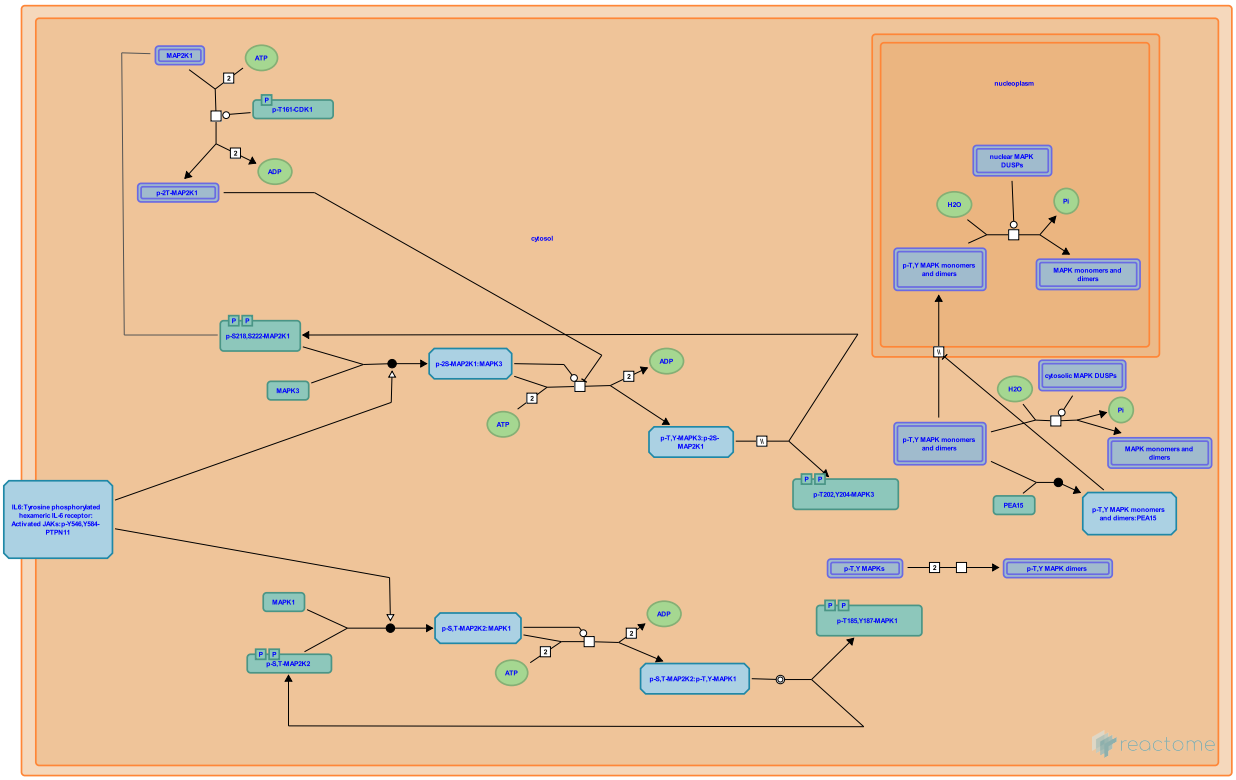
RAF-independent MAPK1/3 activation



Charalambous, M., Greene, LA., Roskoski, R Jr., Rothfels, K., Schmidt, EE.

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

19/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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

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

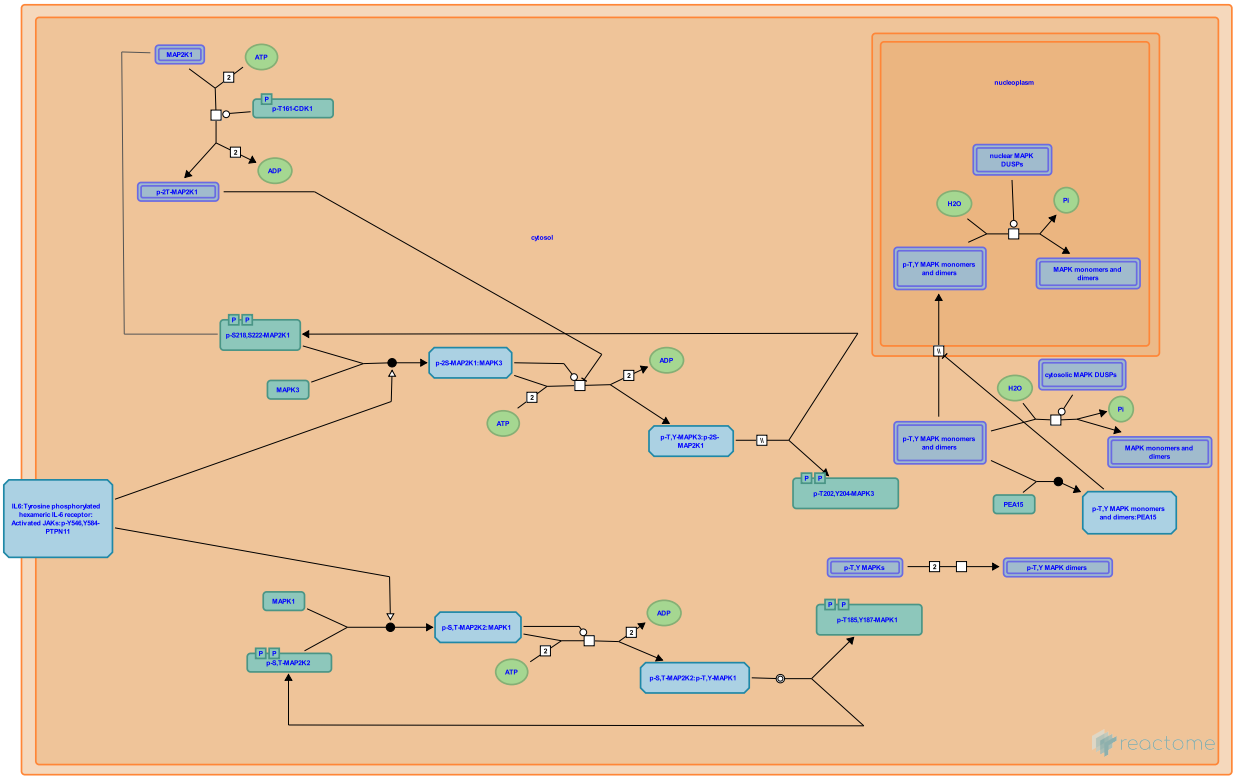
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

RAF-independent MAPK1/3 activation ↗

Stable identifier: R-HSA-112409

Compartments: cytosol, nucleoplasm



Depending upon the stimulus and cell type mitogen-activated protein kinases (MAPK) signaling pathway can transmit signals to regulate many different biological processes by virtue of their ability to target multiple effector proteins (Kyriakis JM & Avruch J 2012; Yoon and Seger 2006; Shaul YD & Seger R 2007; Arthur JS & Ley SC 2013). In particular, the extracellular signal-regulated kinases MAPK3(ERK1) and MAPK1 (ERK2) are involved in diverse cellular processes such as proliferation, differentiation, regulation of inflammatory responses, cytoskeletal remodeling, cell motility and invasion through the increase of matrix metalloproteinase production (Viala E & Pouyssegur J 2004; Hsu MC et al. 2006; Dawson CW et al.2008; Kuriakose T et al. 2014).The canonical RAF:MAP2K:MAPK1/3 cascade is stimulated by various extracellular stimuli including hormones, cytokines, growth factors, heat shock and UV irradiation triggering the GEF-mediated activation of RAS at the plasma membrane and leading to the activation of the RAF MAP3 kinases. However, many physiological and pathological stimuli have been found to activate MAPK1/3 independently of RAF and RAS (Dawson CW et al. 2008; Wang J et al. 2009; Kuriakose T et al. 2014). For example, AMP-activated protein kinase (AMPK), but not RAF1, was reported to regulate MAP2K1/2 and MAPK1/3 (MEK and ERK) activation in rat hepatoma H4IIE and human erythroleukemia K562 cells in response to autophagy stimuli (Wang J et al. 2009). Tumor progression locus 2 (TPL2, also known as MAP3K8 and COT) is another MAP3 kinase which promotes MAPK1/3 (ERK)-regulated immune responses downstream of toll-like receptors (TLR), TNF receptor and IL1beta signaling pathways (Gantke T et al. 2011).

In response to stimuli the cell surface receptors transmit signals inducing MAP3 kinases, e.g., TPL2, MEKK1, which in turn phosphorylate MAP2Ks (MEK1/2). MAP2K then phosphorylate and activate the MAPK1/3 (ERK1 and ERK2 MAPKs). Activated MAPK1/3 phosphorylate and regulate the activities of an ever growing pool of substrates that are estimated to comprise over 160 proteins (Yoon and Seger 2006). The majority of ERK substrates are nuclear proteins, but others are found in the cytoplasm and other organelles. Activated MAPK1/3 can translocate to the nucleus, where they phosphorylate and regulate various transcription factors, such as Ets family transcription factors (e.g., ELK1), ultimately leading to changes in gene expression (Zuber J et al. 2000).

Literature references

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

Ley, SC., Arthur, JS. (2013). Mitogen-activated protein kinases in innate immunity. *Nat. Rev. Immunol., 13*, 679-92. ↗

Ley, SC., Sriskantharajah, S., Gantke, T. (2011). Regulation and function of TPL-2, an I?B kinase-regulated MAP kinase kinase kinase. *Cell Res., 21*, 131-45. ↗

Editions

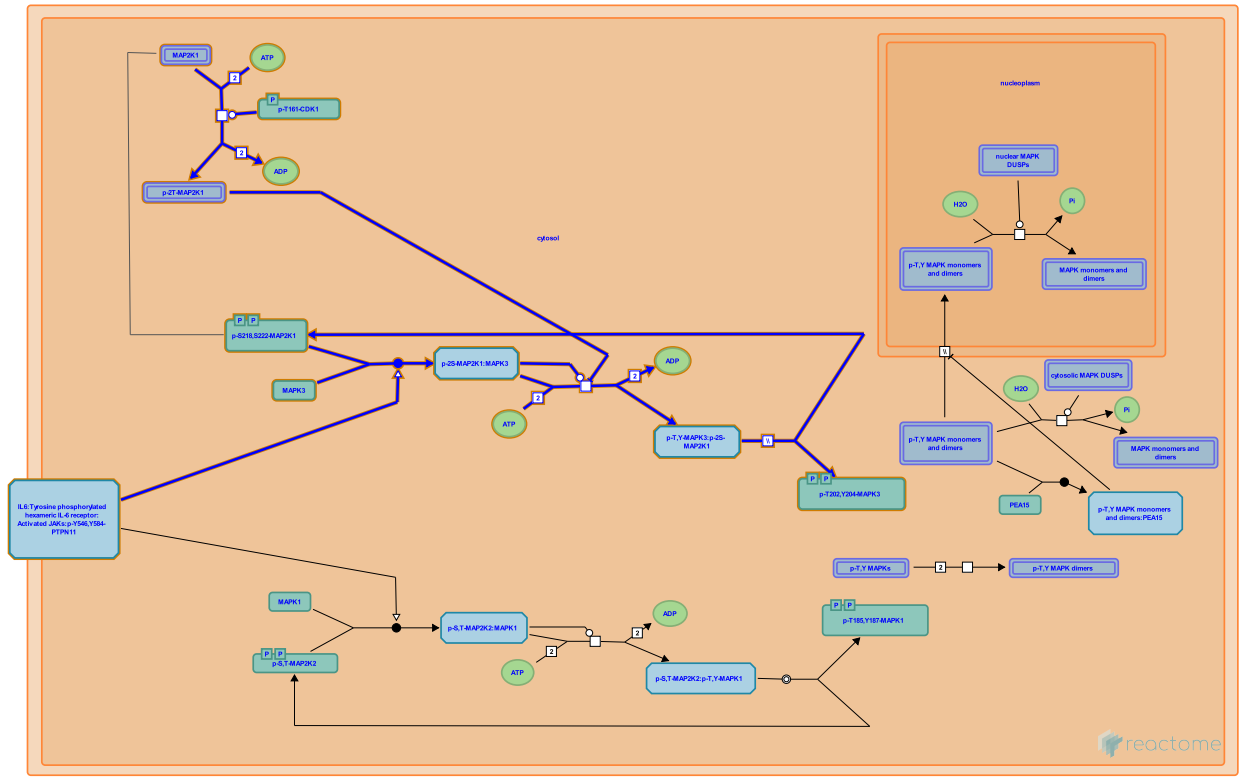
2007-11-08	Reviewed	Greene, LA.

MAPK3 (ERK1) activation ↗

Location: RAF-independent MAPK1/3 activation

Stable identifier: R-HSA-110056

Compartments: nucleoplasm, cytosol



Mitogen-activated protein kinase kinase MAP2K1 (also known as MEK1) is a dual threonine and tyrosine recognition kinase that phosphorylates and activates MAPK3 (ERK1) (Ohren et al. 2004; Roskoski 2012a).

Editions

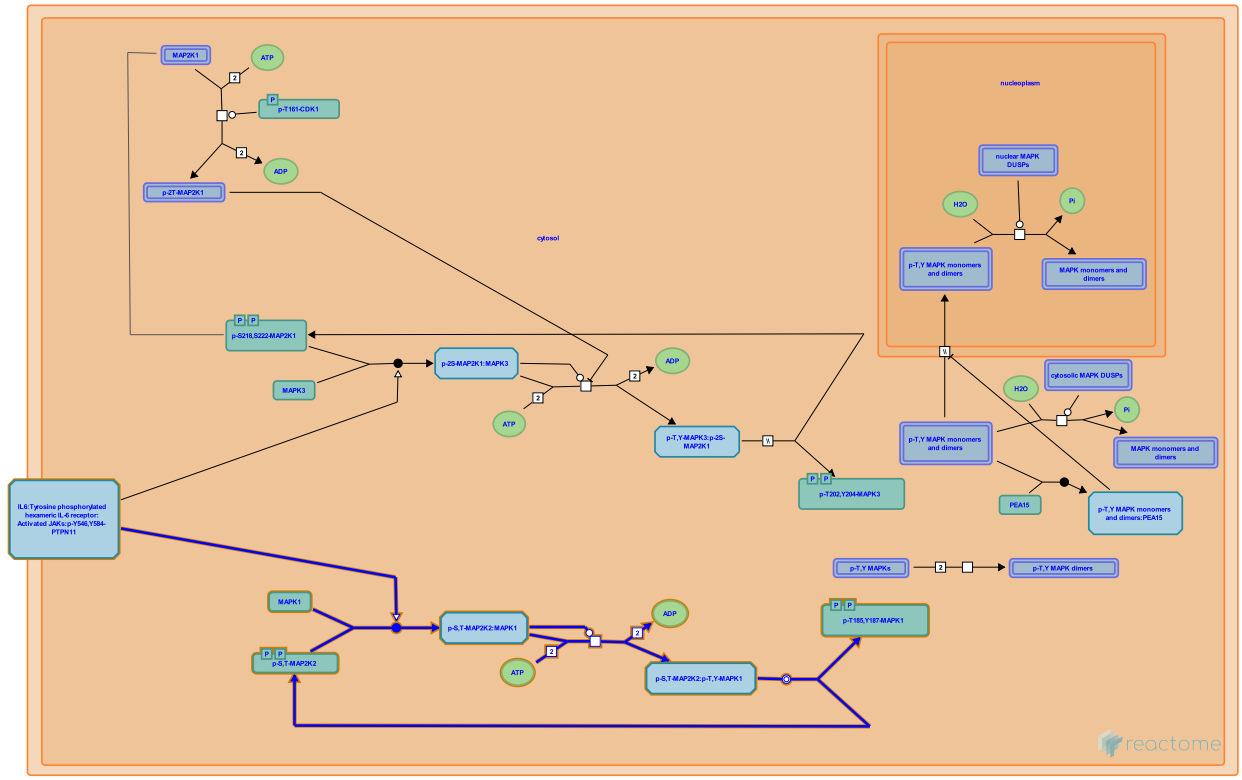
2005-02-04	Authored	Charalambous, M.
2007-11-08	Reviewed	Greene, LA.
2024-03-06	Edited	Schmidt, EE.

MAPK1 (ERK2) activation ↗

Location: RAF-independent MAPK1/3 activation

Stable identifier: R-HSA-112411

Compartments: nucleoplasm, cytosol



Mitogen-activated protein kinase kinase MAP2K2 (also known as MEK2) is a dual threonine and tyrosine recognition kinase that phosphorylates and activates MAPK1 (ERK2) (Ohren et al. 2004; Roskoski 2012).

Literature references

Roskoski, R Jr. (2012). MEK1/2 dual-specificity protein kinases: structure and regulation. *Biochem. Biophys. Res. Commun., 417*, 5-10. ↗

Zheng, CF., Guan, KL. (1994). Activation of MEK family kinases requires phosphorylation of two conserved Ser/Thr residues. *EMBO J, 13*, 1123-31. ↗

Editions

2005-02-04	Authored	Charalambous, M.
2007-11-08	Reviewed	Greene, LA.
2024-03-06	Edited	Schmidt, EE.

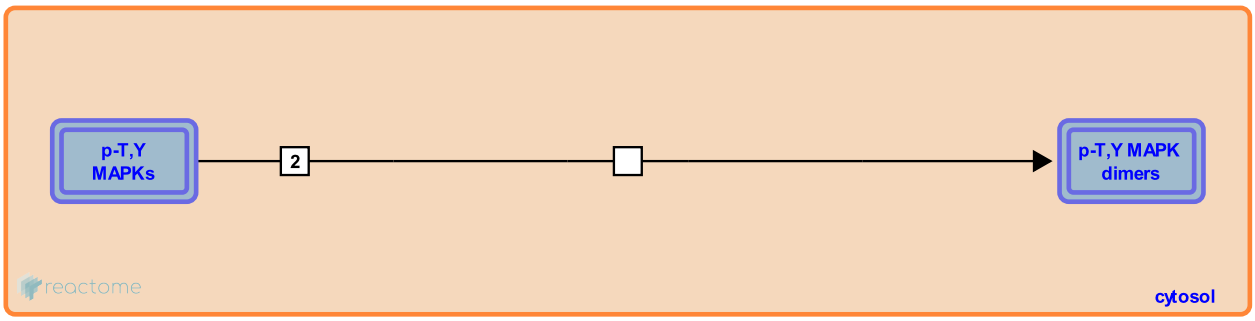
p-T,Y MAPKs dimerize ↗

Location: RAF-independent MAPK1/3 activation

Stable identifier: R-HSA-5674385

Type: transition

Compartments: cytosol



Phosphorylated MAPK monomers can dimerize - generally into MAPK1 and MAPK3 homodimers, as the heterodimer is unstable- but the physiological significance of dimerization is unclear (Khokhlatchev et al, 1998; reviewed Rosokoski, 2012b). MAPKs have both cytosolic and nuclear targets and dimerization may be particularly important for MAPK-dependent phosphorylation of cytosolic targets. Phosphorylation of cytosolic MAPK targets appears to happen predominantly in the context of larger scaffolding complexes, and since the scaffolds and cytosolic MAPK substrates contact the same hydrophobic surface of MAPK, dimerization is necessary to allow assembly of a functional complex (Casar et al, 2008; Lidke et al, 2010; reviewed in Casar et al, 2009). Consistent with this, disrupting either MAPK dimerization or the MAPK interaction with the scaffolding protein abrogated proliferation and transformation (Casar et al, 2008). Note that, for simplicity in this diagram, dimerization is shown as happening between free cytosolic monomers of activated MAPK rather than in the context of the scaffolding complex.
Although predominantly cytoplasmic in resting cells, a proportion of activated MAPK translocates to the nucleus upon stimulation where it activates nuclear targets. Despite early studies to the suggesting that dimerization was required for nuclear translocation, a few recent papers have challenged this notion (Lenormand et al, 1993; Chen et al, 1992; Khokhlatchev et al, 1998; Casar et al, 2008; Lidke et al, 2010; Burack and Shaw, 2005; reviewed in Roskoski, 2012b).

Followed by: Phosphorylated MAPKs translocate into the nucleus, PEA15 binds MAPK monomers and dimers, Cytosolic DUSPs dephosphorylate MAPKs

Literature references

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

Sarnecki, C., Blenis, J., Chen, RH. (1992). Nuclear localization and regulation of erk- and rsk-encoded protein kinases . *Mol. Cell. Biol., 12*, 915-27. ↗

Brunet, A., Pouysségur, J., Pagès, G., L'Allemain, G., Sardet, C., Lenormand, P. (1993). Growth factors induce nuclear translocation of MAP kinases (p42mapk and p44mapk) but not of their activator MAP kinase kinase (p45mapkk) in fibroblasts. *J. Cell Biol., 122*, 1079-88. ↗

Crespo, P., Pinto, A., Casar, B. (2008). Essential role of ERK dimers in the activation of cytoplasmic but not nuclear substrates by ERK-scaffold complexes. *Mol. Cell, 31*, 708-21. ↗

Burack, WR., Shaw, AS. (2005). Live Cell Imaging of ERK and MEK: simple binding equilibrium explains the regulated nucleocytoplasmic distribution of ERK. *J. Biol. Chem., 280*, 3832-7. ↗

Editions

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

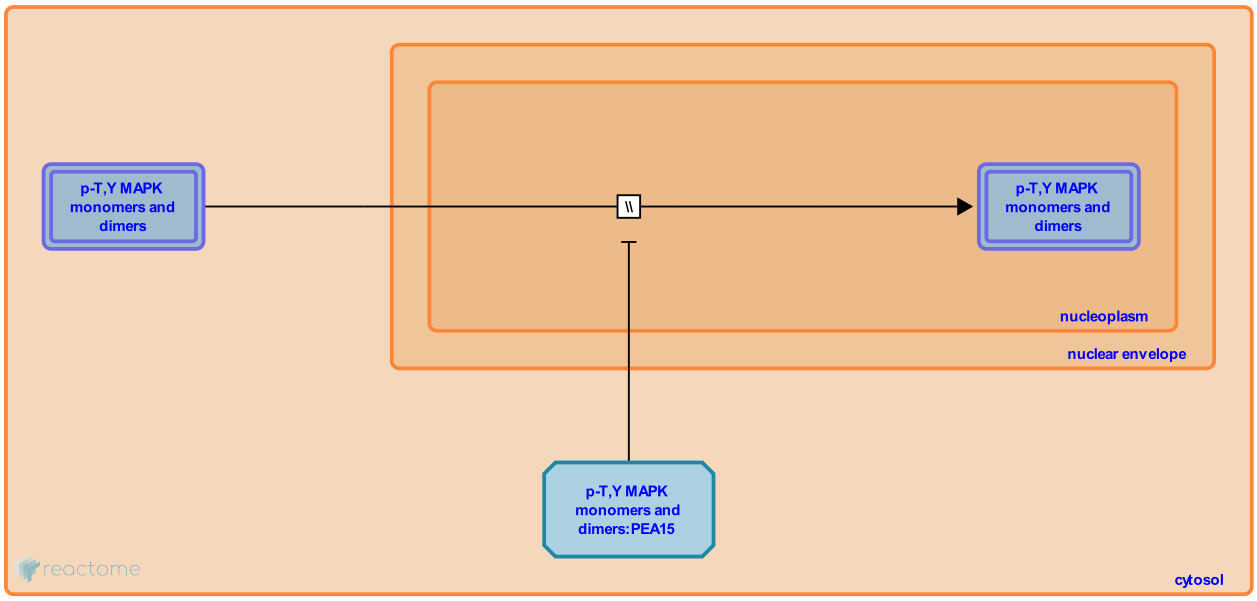
Phosphorylated MAPKs translocate into the nucleus ↗

Location: RAF-independent MAPK1/3 activation

Stable identifier: R-HSA-5674387

Type: omitted

Compartments: nucleoplasm



After phosphorylation by MAP2Ks, a proportion of activated MAPK translocates into the nucleus where it activates nuclear targets (reviewed in Roskoski, 2012b). MAPKs, which lack a nuclear localization signal (NLS), may 'piggyback' into the nucleus in complex with other nuclear-targeted proteins or may translocate by virtue of interaction with components of the nuclear pore complex (Brunet et al, 1999; Adachi et al, 1999; Matsubayashi et al, 2001; Whitehurst et al, 2002; Khokhlatchev et al, 1998; reviewed in Roskoski, 2012b). Although dimerization of MAPKs was thought to be critical for nuclear translocation, a number of studies have now challenged the physiological relevance of MAPK dimerization and this remains an area of uncertainty (Lenormand et al, 1993; Chen et al, 1992; Casar et al, 2008; Lidke et al, 2010; Burack and Shaw, 2005; reviewed in Casar et al, 2009; Roskoski, 2012b)

Preceded by: p-T,Y MAPKs dimerize

Followed by: Nuclear DUSPs dephosphorylate MAPKs

Literature references

Brunet, A., Dowd, S., Pouysségur, J., Keyse, S., Roux, D., Lenormand, P. (1999). Nuclear translocation of p42/p44 mitogen-activated protein kinase is required for growth factor-induced gene expression and cell cycle entry. *EMBO J., 18*, 664-74. ↗

Crespo, P., Pinto, A., Casar, B. (2009). ERK dimers and scaffold proteins: unexpected partners for a forgotten (cytoplasmic) task. *Cell Cycle, 8*, 1007-13. ↗

Jovin, TM., Pouysségur, J., Post, JN., Huang, F., Rieger, B., Thomas, JL. et al. (2010). ERK nuclear translocation is dimerization-independent but controlled by the rate of phosphorylation. *J. Biol. Chem., 285*, 3092-102. ↗

Cobb, MH., Atkinson, M., Goldsmith, E., Wilsbacher, J., Robinson, M., Khokhlatchev, AV. et al. (1998). Phosphorylation of the MAP kinase ERK2 promotes its homodimerization and nuclear translocation. *Cell, 93*, 605-15. ↗

You, Y., Cobb, MH., Wilsbacher, JL., Moore, MS., Luby-Phelps, K., Whitehurst, AW. (2002). ERK2 enters the nucleus by a carrier-independent mechanism. *Proc. Natl. Acad. Sci. U.S.A., 99*, 7496-501. ↗

Editions

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

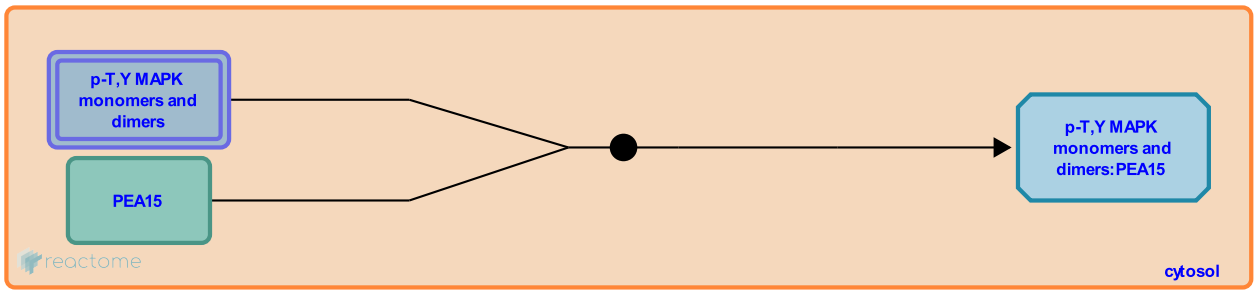
PEA15 binds MAPK monomers and dimers ↗

Location: RAF-independent MAPK1/3 activation

Stable identifier: R-HSA-5675206

Type: binding

Compartments: cytosol



PEA15 is a cytoplasmic anchor that binds directly to activated MAPKs prevents their translocation into the nucleus (Formstecher et al, 2001; Whitehurst et al, 2004; Hill et al, 2002; Chou et al, 2003). PEA15 also protects phosphorylated MAPKs in the cytoplasm from inactivating dephosphorylation (Mace et al, 2013). In this way, binding of PEA15 promotes phosphorylation of cytoplasmic MAPK targets at the expense of nuclear ones.

Preceded by: p-T,Y MAPKs dimerize

Literature references

Ginsberg, MH., Uberall, F., Brunet, A., Ramos, JW., Pouysségur, J., Glading, A. et al. (2003). PEA-15 binding to ERK1/2 MAPKs is required for its modulation of integrin activation. *J. Biol. Chem., 278*, 52587-97. ↗

Ginsberg, MH., Chneiweiss, H., Ramos, JW., Canton, B., Formstecher, E., Nguyen, XT. et al. (2001). PEA-15 mediates cytoplasmic sequestration of ERK MAP kinase. *Dev. Cell, 1*, 239-50. ↗

Cobb, MH., Moore, MS., Robinson, FL., Whitehurst, AW. (2004). The death effector domain protein PEA-15 prevents nuclear entry of ERK2 by inhibiting required interactions. *J. Biol. Chem., 279*, 12840-7. ↗

Robinson, H., Riedl, SJ., Pasquale, EB., Egger, MF., Wallez, Y., Mace, PD. et al. (2013). Structure of ERK2 bound to PEA-15 reveals a mechanism for rapid release of activated MAPK. *Nat Commun, 4*, 1681. ↗

Editions

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

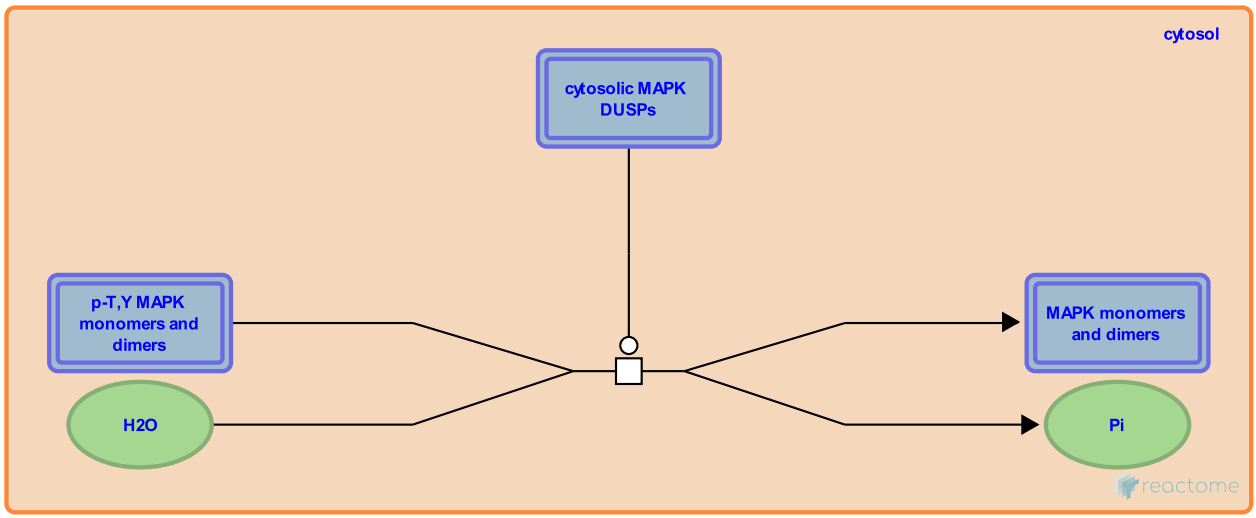
Cytosolic DUSPs dephosphorylate MAPKs ↗

Location: RAF-independent MAPK1/3 activation

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).

Preceded by: p-T,Y MAPKs dimerize

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.

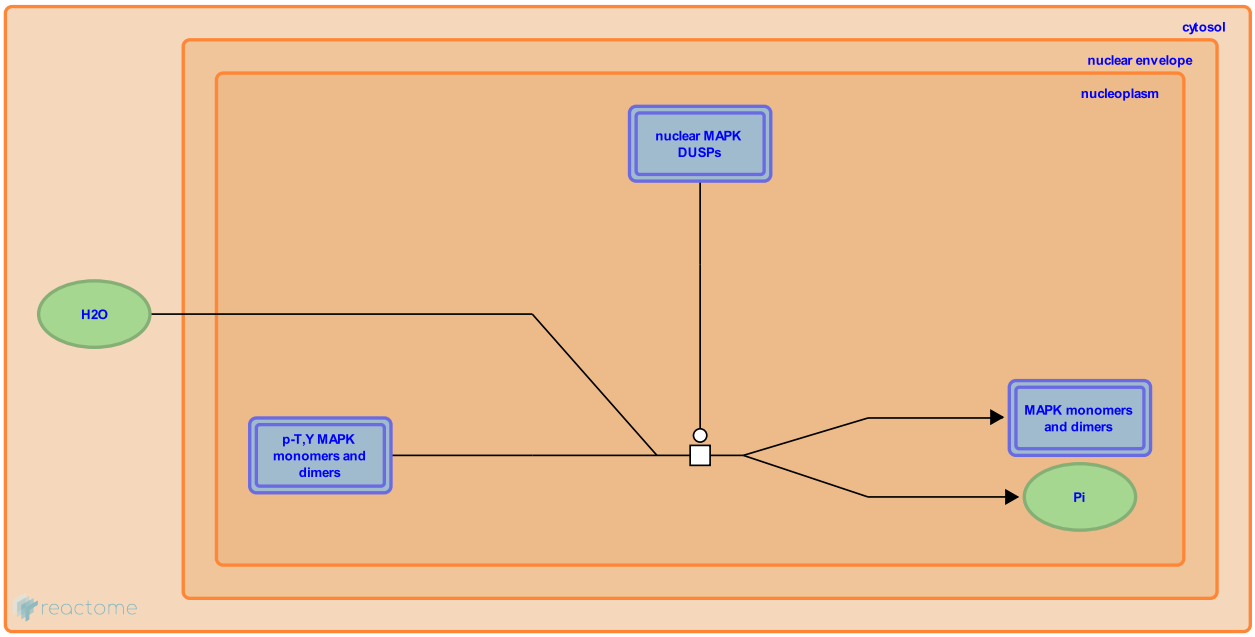
Nuclear DUSPs dephosphorylate MAPKs ↗

Location: RAF-independent MAPK1/3 activation

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).

Preceded by: Phosphorylated MAPKs translocate into the nucleus

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.

Table of Contents

Introduction 1

RAF-independent MAPK1/3 activation 2

MAPK3 (ERK1) activation 4

MAPK1 (ERK2) activation 5

p-T,Y MAPKs dimerize 6

Phosphorylated MAPKs translocate into the nucleus 7

PEA15 binds MAPK monomers and dimers 9

Cytosolic DUSPs dephosphorylate MAPKs 10

Nuclear DUSPs dephosphorylate MAPKs 11

Table of Contents 12