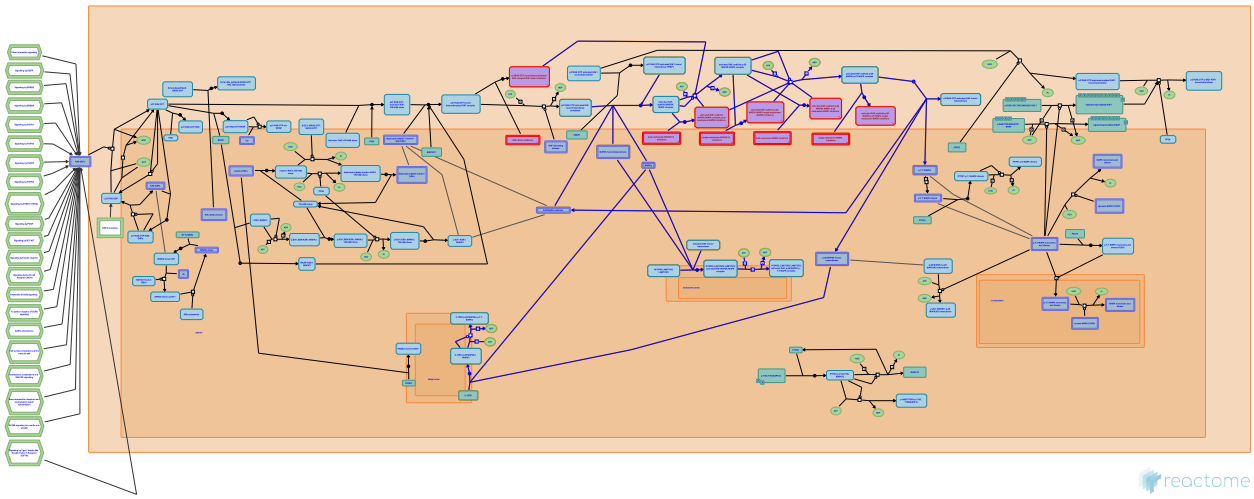
MAP2K and MAPK activation



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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. ↗

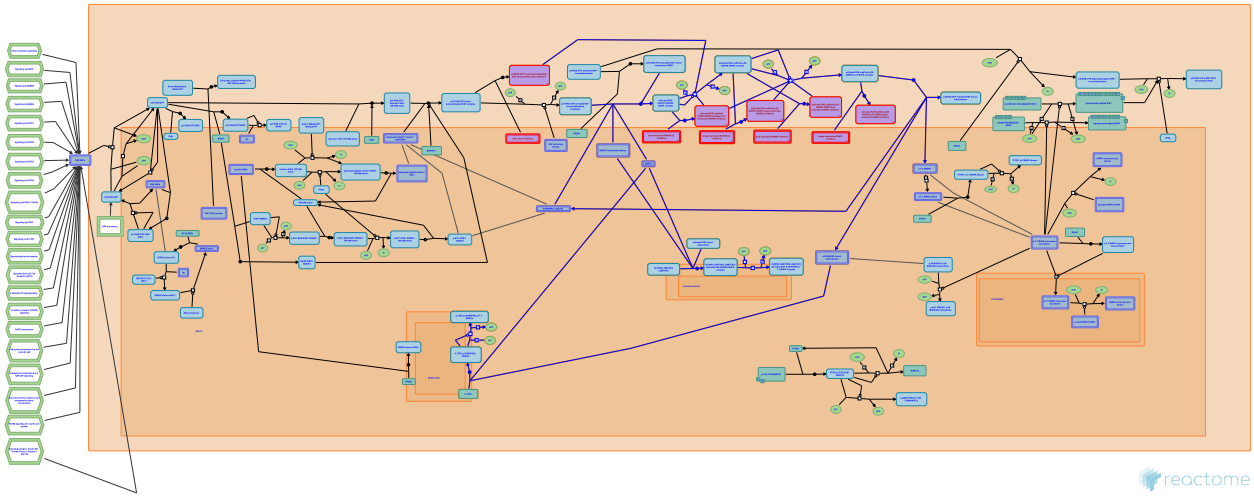
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

MAP2K and MAPK activation ↗

Stable identifier: R-HSA-5674135



Activated RAF proteins are restricted substrate kinases whose primary downstream targets are the two MAP2K proteins, MAPK2K1 and MAP2K2 (also known as MEK1 and MEK2) (reviewed in Roskoski, 2010, Roskoski, 2012a). Phosphorylation of the MAPK2K activation loop primes them to phosphorylate the primary effector of the activated MAPK pathway, the two MAPK proteins MAPK3 and MAPK1 (also known as ERK1 and 2). Unlike their upstream counterparts, MAPK3 and MAPK1 catalyze the phosphorylation of hundreds of cytoplasmic and nuclear targets including transcription factors and regulatory molecules (reviewed in Roskoski, 2012b). Activation of MAP2K and MAPK proteins downstream of activated RAF generally occurs in the context of a higher order scaffolding complex that regulates the specificity and localization of the pathway (reviewed in Brown and Sacks, 2009; Matallanas et al, 2011).

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. ↗

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

Roskoski, R Jr. (2010). RAF protein-serine/threonine kinases: structure and regulation. *Biochem. Biophys. Res. Commun., 399*, 313-7. ↗

Brown, MD., Sacks, DB. (2009). Protein scaffolds in MAP kinase signalling. *Cell. Signal., 21*, 462-9. ↗

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

Editions

2015-02-10	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

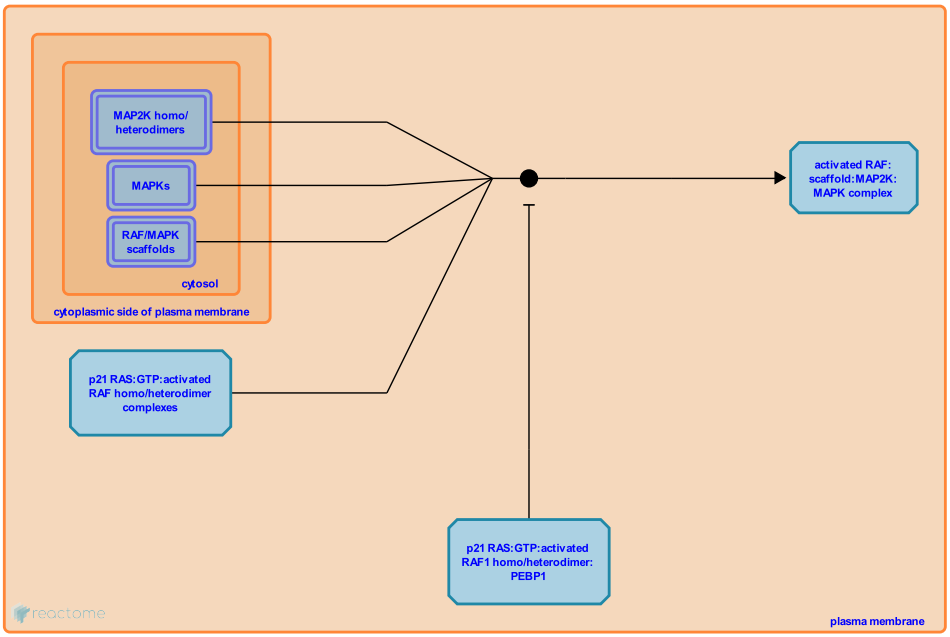
MAP2Ks and MAPKs bind to the activated RAF complex ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5672972

Type: binding

Compartments: plasma membrane



RAF kinases have restricted substrate specificity and have as their primary substrates the two MAP2K proteins MAP2K1 and MAP2K2 (also known as MEK1 and 2). MAP2K1 knockout is embryonic lethal in mice, while MAP2K2 knockouts have no apparent abnormalities, suggesting that MAP2K1 can compensate for MAP2K2 in vivo (Giroux et al, 1999; Belanger et al, 2003). MAP2K proteins exist as stable homo- and heterodimers independent of growth factor stimulation and are generally recruited to activated RAF proteins in conjunction with a scaffolding protein and the MAP2K substrates, MAPK1 and 3 (also known as ERK1 and 2) (Ohren et al, 2004; Catalanotti et al, 2009; Catling et al, 1995; reviewed in Matallanas et al, 2011; Roskoski et al, 2012a; Roskoski et al, 2012b).

Scaffolding proteins promote signaling by providing a docking platform that colocalizes components of the signaling cascade, and provide specificity by controlling the spatial and temporal regulation of the pathway (reviewed in Brown and Sacks, 2009; Matallanas et al, 2011). KSR1 and 2, CNKSR1 and 2, IQGAP1 and the beta arrestins are among the known MAPK scaffold proteins that act at the plasma membrane upon MAPK pathway activation; in addition, paxillin localizes MAPK pathway components to focal adhesion sites in the plasma membrane (Roy et al, 2005; Ren et al, 2007; DeFea et al, 2000; Togho et al, 2003; Ishibe et al, 2003; reviewed in Claperon and Therrien, 2007; Brown and Sacks, 2009; Matallanas et al, 2011). Although this reaction depicts these scaffolding proteins acting equivalently, the details of how they promote pathway activation vary. For instance, KSR1 and 2 are constitutively bound to MAP2K dimers but recruit MAPKs only upon pathway stimulation, while IQGAP1 associates constitutively with both MAP2K and MAPK proteins in unstimulated cells and shows increased interaction with MAP2K1 upon pathway activation by EGF (Stewart et al, 1999; Cacace et al, 2000; Muller et al, 2000; Roy et al, 2004; Roy et al, 2005; reviewed in Brown and Sacks, 2009). Scaffolding complexes may be particularly important for the phosphorylation of cytosolic MAPK targets (reviewed in Casar et al, 2009).

Followed by: RAF phosphorylates MAP2K dimer, Dual mechanism MAP2K inhibitors bind MAP2Ks

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. ↗

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

Mullins, RD., Zalevsky, J., Bunnett, NW., DeFea, KA., Déry, O., Thoma, MS. (2000). beta-arrestin-dependent endocytosis of proteinase-activated receptor 2 is required for intracellular targeting of activated ERK1/2. *J. Cell Biol., 148*, 1267-81. ↗

Oakley, RH., Caron, MG., Luttrell, LM., Gesty-Palmer, D., Pierce, KL., Laporte, S. et al. (2003). The stability of the G protein-coupled receptor-beta-arrestin interaction determines the mechanism and functional consequence of ERK activation. *J. Biol. Chem., 278*, 6258-67. ↗

Rubin, GM., Copeland, T., Cacace, AM., Morrison, DK., Mathes, K., Michaud, NR. et al. (1999). Identification of constitutive and ras-inducible phosphorylation sites of KSR: implications for 14-3-3 binding, mitogen-activated protein kinase binding, and KSR overexpression. *Mol Cell Biol, 19*, 229-40. ↗

Editions

2014-12-18	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

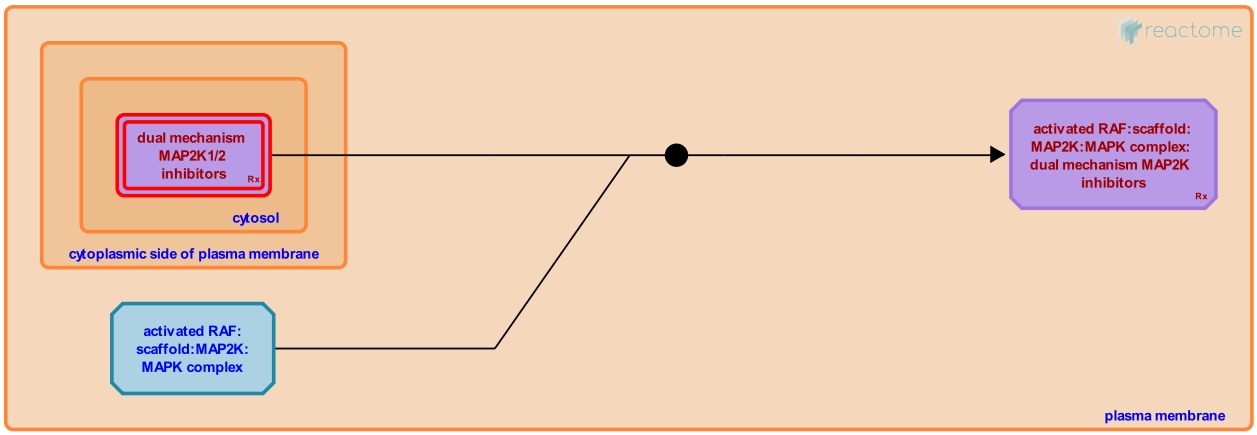
Dual mechanism MAP2K inhibitors bind MAP2Ks ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-9657599

Type: binding

Compartments: plasma membrane, cytosol



Although mutations in MAP2K proteins are infrequent in human cancers, the position of these kinases downstream of RAS and RAF make them good candidates for therapeutic targeting. Dual mechanism inhibitors such as trametinib bind to non-phosphorylated MAP2K proteins, inhibiting their MAPK-directed kinase activity as well as preventing their phosphorylation by RAF proteins (Hatzivassiliou et al, 2013; Lito et al, 2014; Ishii et al, 2013; reviewed in Samatar and Poulikakos, 2014).

Preceded by: MAP2Ks and MAPKs bind to the activated RAF complex

Literature references

Lukacs, C., Morikami, K., Solomon, M., Gadal, S., Lowe, S., Ohara, K. et al. (2014). Disruption of CRAF-mediated MEK activation is required for effective MEK inhibition in KRAS mutant tumors. *Cancer Cell, 25*, 697-710. ↗

Sakai, T., Shimma, N., Tomii, Y., Sowa, Y., Tachibana-Kondo, Y., Aoki, T. et al. (2013). Enhanced inhibition of ERK signaling by a novel allosteric MEK inhibitor, CH5126766, that suppresses feedback reactivation of RAF activity. *Cancer Res., 73*, 4050-4060. ↗

Merchant, M., Haling, JR., Luoh, SM., Wiesmann, C., Price, S., Heald, R. et al. (2013). Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. *Nature, 501*, 232-6. ↗

Poulikakos, PI., Samatar, AA. (2014). Targeting RAS-ERK signalling in cancer: promises and challenges. *Nat Rev Drug Discov, 13*, 928-42. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

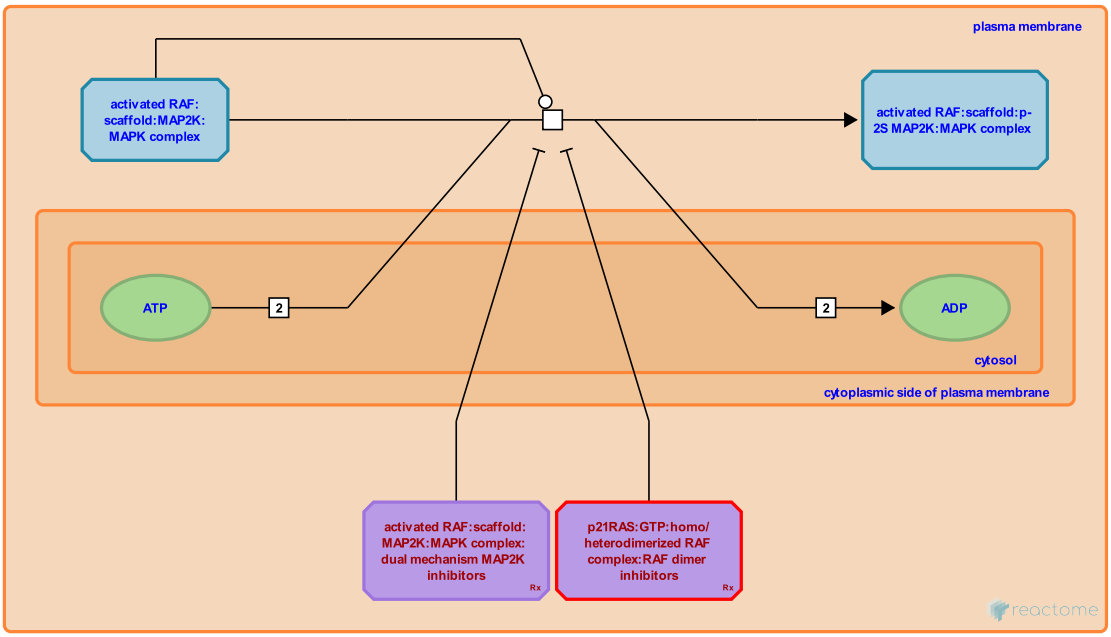
RAF phosphorylates MAP2K dimer ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5672978

Type: transition

Compartments: plasma membrane



Activated RAF phosphorylates the MEK kinases MAP2K1 and MAP2K2 on 2 serine residues in the MAP2K activation loop (S218 and S222 in MAP2K1 and S222 and S226 in MAP2K2 (Zheng and Guan, 1994; Alessi et al, 1994; Catling et al, 1995; Papin et al, 1995; Seger et al, 1994; reviewed in Roskoski, 2012a). Although all three RAF kinases can phosphorylate MAP2K1 and MAP2K2, BRAF appears to be the primary activator in vivo (Marais et al, 1997; Jaiswal et al, 1994; Pritchard et al, 1995; reviewed in Welbrock et al, 2004)

Preceded by: MAP2Ks and MAPKs bind to the activated RAF complex

Followed by: Single mechanism MAP2K inhibitors bind phosphorylated MAP2Ks, Dual mechanism MAPK inhibitors bind MAPKs, MAP2Ks phosphorylate MAPKs

Literature references

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

Bosch, E., McMahon, M., Samuels, ML., Pritchard, CA. (1995). Conditionally oncogenic forms of the A-Raf and B-Raf protein kinases display different biological and biochemical properties in NIH 3T3 cells. *Mol. Cell. Biol., 15*, 6430-42. ↗

Seger, D., Reszka, AA., Seger, R., Krebs, EG., Campbell, JS., Fischer, EH. et al. (1994). Overexpression of mitogen-activated protein kinase kinase (MAPKK) and its mutants in NIH 3T3 cells. Evidence that MAPKK involvement in cellular proliferation is regulated by phosphorylation of serine residues in its kinase subdomains VII and VIII. *J Biol Chem, 269*, 25699-709. ↗

Reddy, GR., Weber, MJ., Schaeffer, HJ., Reuter, CW., Catling, AD. (1995). A proline-rich sequence unique to MEK1 and MEK2 is required for raf binding and regulates MEK function. *Mol Cell Biol, 15*, 5214-25. ↗

Barnier, JV., Pouysségur, J., Calothy, G., Brunet, A., Pagès, G., Papin, C. et al. (1995). B-Raf protein isoforms interact with and phosphorylate Mek-1 on serine residues 218 and 222. *Oncogene, 10*, 1647-51. ↗

Editions

2014-12-18	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

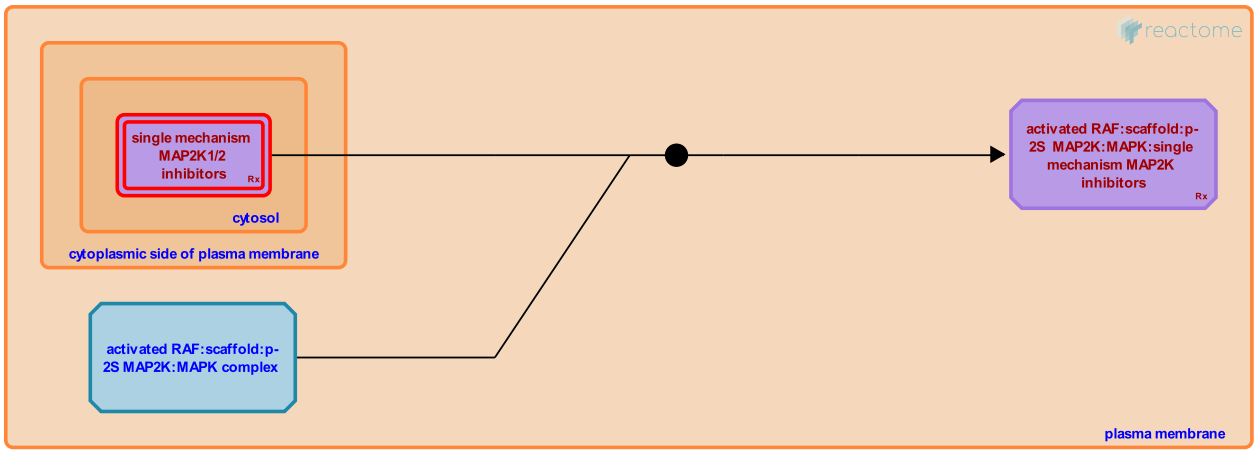
Single mechanism MAP2K inhibitors bind phosphorylated MAP2Ks ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-9657606

Type: binding

Compartments: plasma membrane, cytosol



Single mechanism MAP2K inhibitors bind to phosphorylated forms of MAP2K 1 and 2 and prevent their phosphorylation of MAPK proteins (Hatzivassiliou et al, 2013; reviewed in Samatar and Poulikakos, 2014).

Preceded by: RAF phosphorylates MAP2K dimer

Literature references

Merchant, M., Haling, JR., Luoh, SM., Wiesmann, C., Price, S., Heald, R. et al. (2013). Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. *Nature, 501*, 232-6. ↗

Poulikakos, PI., Samatar, AA. (2014). Targeting RAS-ERK signalling in cancer: promises and challenges. *Nat Rev Drug Discov, 13*, 928-42. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

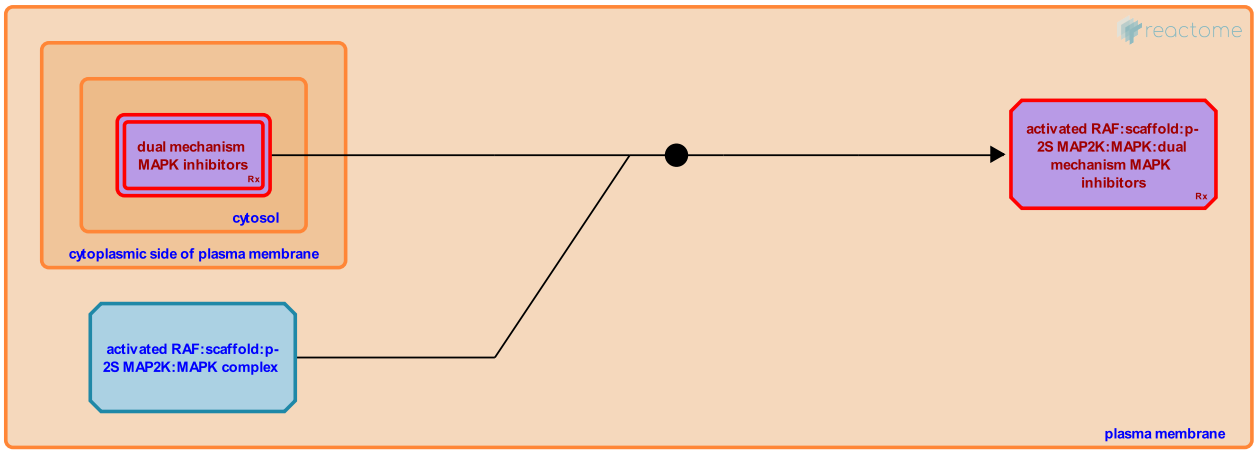
Dual mechanism MAPK inhibitors bind MAPKs ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-9657603

Type: binding

Compartments: plasma membrane, cytosol



A number of 'dual mechanism' MAPK inhibitors are in preclinical or clinical trials (reviewed in Roskoski, 2019). Dual mechanism inhibitors, including the ATP-competitive inhibitors SCH772984 and MK-8353, bind to the unphosphorylated MAPK and prevent both its own kinase activity and its phosphorylation by MAP2Ks (Morris et al, 2013; Deng et al 2014; Chaikuad et al, 2014; Boga et al, 2018; Moschos et al, 2019; reviewed in Samatar and Poulikakos, 2014). MAPK inhibitors offer the potential to mitigate the development of resistance to RAF and MAP2K inhibitors, which often involves reactivation of MAPK-dependent signaling. As a result, MAPK inhibitors are frequently used in combination with RAF and MAP2K-directed therapeutics (reviewed in Samatar and Poulikakos, 2014; Roskoski, 2019).

Preceded by: RAF phosphorylates MAP2K dimer

Literature references

Alhassan, AB., Paliwal, S., Desai, J., Dayananth, P., Zhu, H., Samatar, AA. et al. (2018). MK-8353: Discovery of an Orally Bioavailable Dual Mechanism ERK Inhibitor for Oncology. *ACS Med Chem Lett, 9*, 761-767. ↗

Liang, Y., Knapp, S., Chaikuad, A., Tacconi, EM., Zimmer, J., Gray, NS. et al. (2014). A unique inhibitor binding site in ERK1/2 is associated with slow binding kinetics. *Nat. Chem. Biol., 10*, 853-60. ↗

Liu, J., Fawell, S., Angagaw, MH., Paliwal, S., Zawel, L., Desai, J. et al. (2013). Discovery of a novel ERK inhibitor with activity in models of acquired resistance to BRAF and MEK inhibitors. *Cancer Discov, 3*, 742-50. ↗

Roskoski, R Jr. (2019). Targeting ERK1/2 protein-serine/threonine kinases in human cancers. *Pharmacol. Res., 142*, 151-168. ↗

English, JM., Nan, Y., Dayananth, P., Zhu, HY., Chuang, CC., Windsor, WT. et al. (2014). Discovery of novel, dual mechanism ERK inhibitors by affinity selection screening of an inactive kinase. *J. Med. Chem., 57*, 8817-26. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

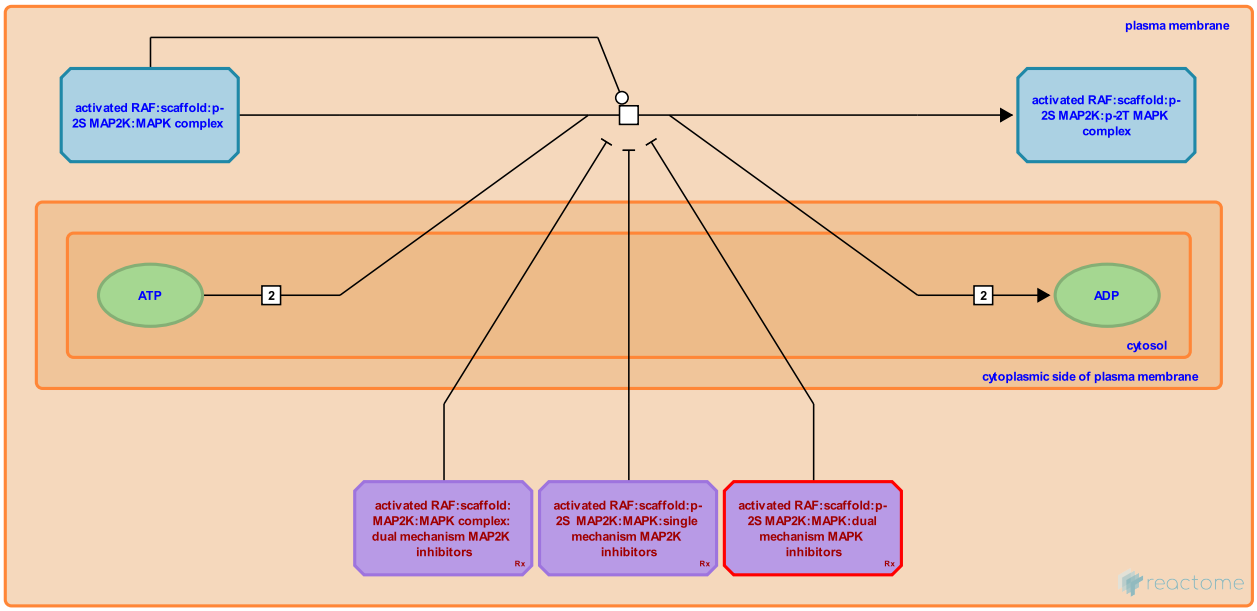
MAP2Ks phosphorylate MAPKs ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5672973

Type: transition

Compartments: plasma membrane



Activated MAP2K phosphorylates MAPK on threonine and tyrosine residues in the activation loop (residues T202 and Y204 in MAPK3, residues T185 and Y187 in MAPK1) (Ray et al, 1988; reviewed in Roskoski, 2012b). MAPK3 and MAPK1 are 84% identical and appear to be stimulated in parallel by all known activators of the MAPK pathway (Lefloch et al, 2009; reviewed in Lloyd, 2006).

Preceded by: RAF phosphorylates MAP2K dimer

Followed by: Single mechanism MAPK inhibitors bind phosphorylated MAPK, Dissociation of RAS:RAF complex

Literature references

Sturgill, TW., Ray, LB. (1988). Insulin-stimulated microtubule-associated protein kinase is phosphorylated on tyrosine and threonine in vivo. *Proc. Natl. Acad. Sci. U.S.A., 85*, 3753-7. ↗

Lloyd, AC. (2006). Distinct functions for ERKs?. *J. Biol., 5*, 13. ↗

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

Pouysségur, J., Lefloch, R., Lenormand, P. (2009). Total ERK1/2 activity regulates cell proliferation. *Cell Cycle, 8*, 705-11. ↗

Editions

2014-12-18	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

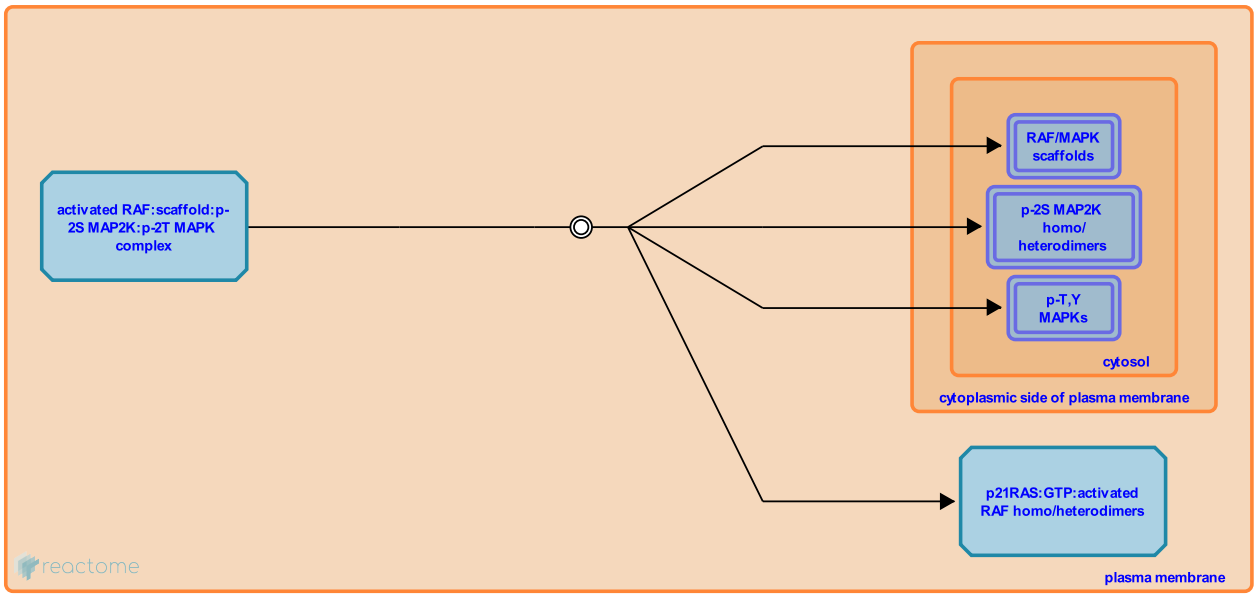
Dissociation of RAS:RAF complex ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5672980

Type: dissociation

Compartments: plasma membrane



The mechanisms governing the dissociation or trafficking of activated MAPK signaling complexes at the plasma membrane are not fully worked out. Some active complexes may be endocytosed and targeted to other cellular locations, for example the Golgi complex (Lorentzen et al, 2010). Activated RAF monomers may dissociate and homo- or heterodimerize with additional inactive RAF monomers and in this way amplify the signal (reviewed in Matallanas et al, 2011; Cseh et al, 2014).
Ultimately, active RAF complexes are subject to PP5- and PP2A-mediated dephosphorylation, which promotes a return to the inactive state. Hydrolysis of RAS-bound GTP by the intrinsic GTPase activity, stimulated by association with RAS GAP proteins, ultimately promotes dissociation of RAS from RAF allowing a return to the quiescent state (reviewed in Wellbrock et al, 2004; Matallanas et al, 2011).

Preceded by: MAP2Ks phosphorylate MAPKs

Followed by: IL17RD binds p-2S MAP2Ks and MAPKs

Literature references

Wellbrock, C., Karasarides, M., Marais, R. (2004). The RAF proteins take centre stage. *Nat Rev Mol Cell Biol, 5*, 875-85. ↗

Baccarini, M., Cseh, B., Doma, E. (2014). "RAF" neighborhood: protein-protein interaction in the Raf/Mek/Erk pathway. *FEBS Lett., 588*, 2398-406. ↗

Lorentzen, A., Bastiaens, PI., Kinkhabwala, A., Vartak, N., Rocks, O. (2010). Regulation of Ras localization by acylation enables a mode of intracellular signal propagation. *Sci Signal, 3*, ra68. ↗

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

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

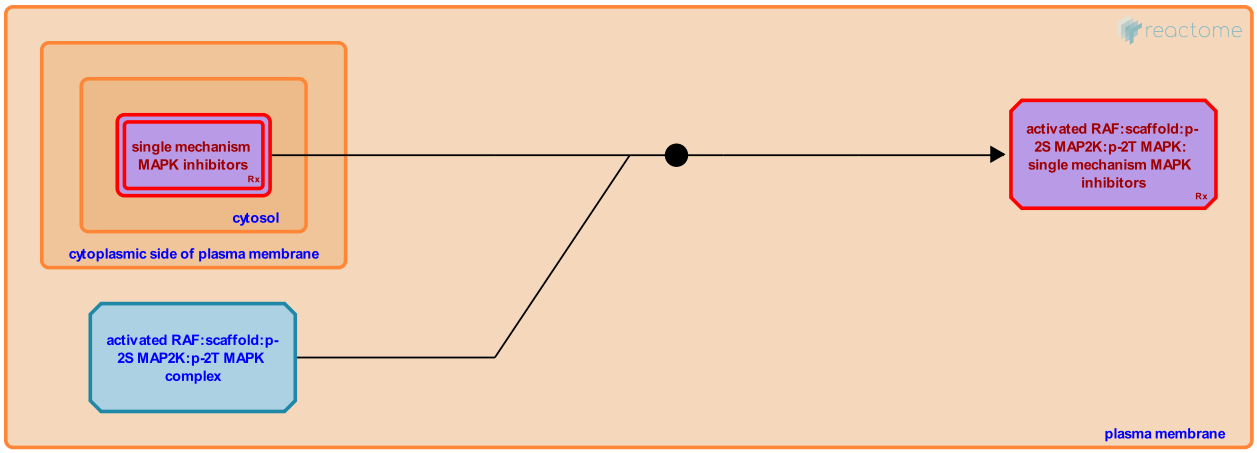
Single mechanism MAPK inhibitors bind phosphorylated MAPK ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-9657608

Type: binding

Compartments: plasma membrane, cytosol



Single mechanism MAPK inhibitors such as ulixertinib and ravoxertinib bind to the activated forms of MAPK proteins and inhibit their intrinsic target-directed kinase activity (Germann et al, 2017; Blake et al, 2016; reviewed in Samatar and Poulikakos, 2014).

Preceded by: MAP2Ks phosphorylate MAPKs

Literature references

Namchuk, M., Germann, UA., Roix, JJ., Shapiro, P., Hoover, RR., Meshaw, K. et al. (2017). Targeting the MAPK Signaling Pathway in Cancer: Promising Preclinical Activity with the Novel Selective ERK1/2 Inhibitor BVD-523 (Ulixertinib). *Mol. Cancer Ther., 16*, 2351-2363. ↗

Ren, L., Yin, J., Wang, W., Robarge, K., Liu, L., Moffat, J. et al. (2016). Discovery of (S)-1-(1-(4-Chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one (GDC-0994), an Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) Inhibitor in Early Clinical Development. *J. Med. Chem., 59*, 5650-60. ↗

Poulikakos, PI., Samatar, AA. (2014). Targeting RAS-ERK signalling in cancer: promises and challenges. *Nat Rev Drug Discov, 13*, 928-42. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

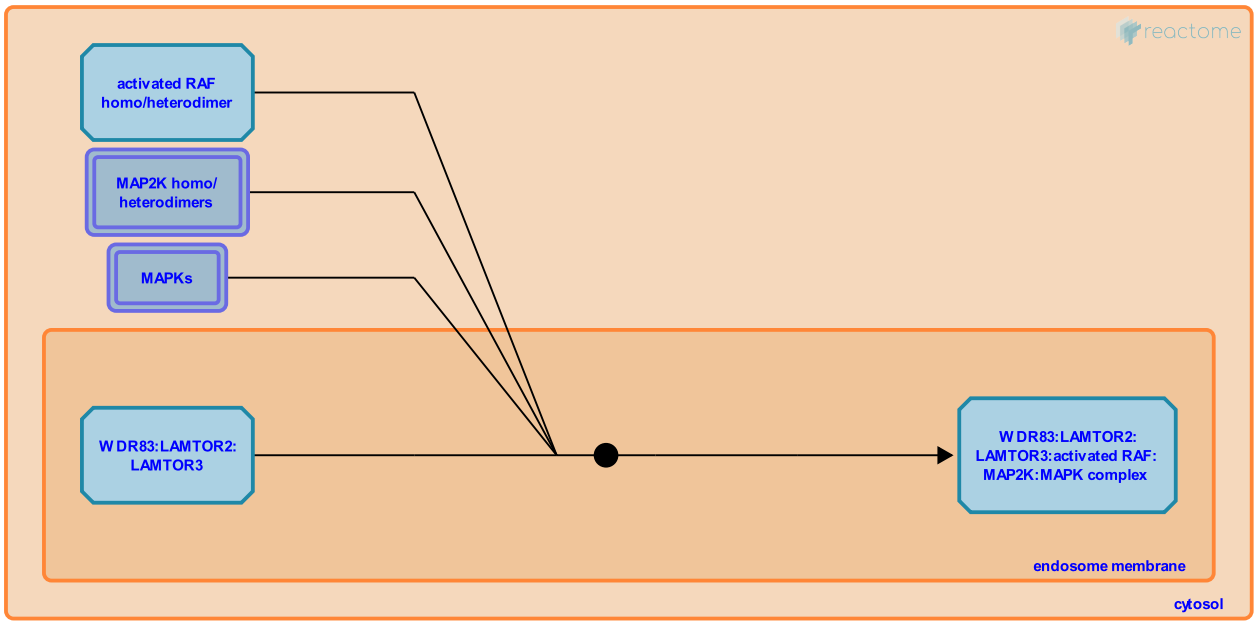
WDR83:LAMTOR2:LAMTOR3 binds MAPK components ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5674132

Type: binding

Compartments: endosome membrane



LAMTOR3 (also known as MEK partner 1, MP1) exists in an obligatory complex with LAMTOR2 (p14) at the endosomal membrane where they act as a scaffold and promote MAPK activation (Schaeffer et al, 1998; Teis et al, 2002; Teis et al, 2006; Sharma et al, 2005). The LAMTOR2/LAMTOR3 complex may also be part of a larger molecular weight complex at the endosome that includes the MAPK organizer protein MORG1 (Vomastek et al, 2004; Sharma et al, 2005; reviewed in Matallanas et al, 2011).

Followed by: MAP2Ks and MAPKs are phosphorylated at the endosome membrane

Literature references

Teis, D., Huber, LA., Wunderlich, W. (2002). Localization of the MP1-MAPK scaffold complex to endosomes is mediated by p14 and required for signal transduction. *Dev. Cell, 3*, 803-14. ↗

Sharma, C., Eblen, ST., Weber, MJ., Catling, AD., Tarcsafalvi, A., Vomastek, T. et al. (2005). MEK partner 1 (MP1): regulation of oligomerization in MAP kinase signaling. *J. Cell. Biochem., 94*, 708-19. ↗

Teis, D., Kurzbauer, R., Villunger, A., de Araujo, ME., Geley, S., Erlacher, M. et al. (2006). p14-MP1-MEK1 signaling regulates endosomal traffic and cellular proliferation during tissue homeostasis. *J. Cell Biol., 175*, 861-8. ↗

Eblen, ST., Weber, MJ., Collier, LS., Catling, AD., Schaeffer, HJ., Krauss, A. (1998). MP1: a MEK binding partner that enhances enzymatic activation of the MAP kinase cascade. *Science, 281*, 1668-71. ↗

Weber, MJ., Tarcsafalvi, A., Vomastek, T., Schaeffer, HJ., Bissonette, EA., Smolkin, ME. (2004). Modular construction of a signaling scaffold: MORG1 interacts with components of the ERK cascade and links ERK signaling to specific agonists. *Proc. Natl. Acad. Sci. U.S.A., 101*, 6981-6. ↗

Editions

2015-02-10	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

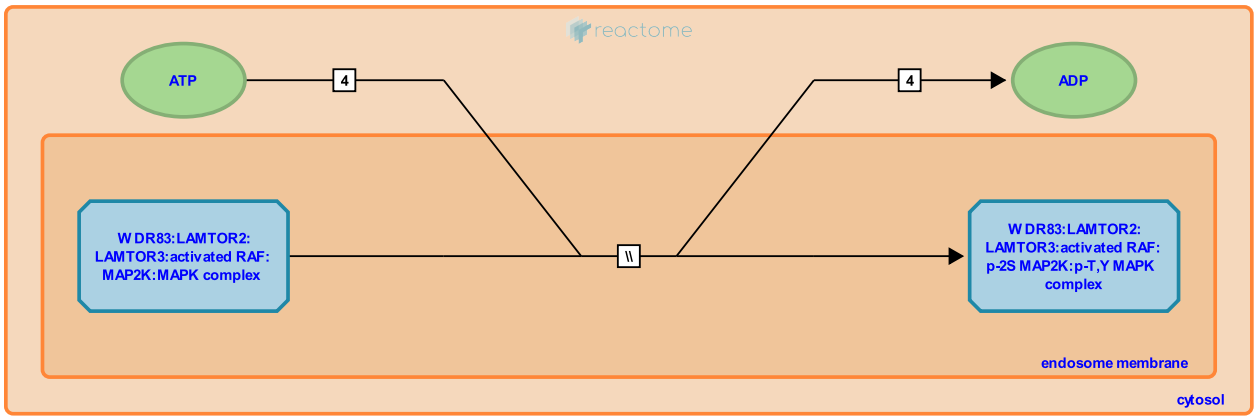
MAP2Ks and MAPKs are phosphorylated at the endosome membrane ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5674130

Type: omitted

Compartments: endosome membrane



Interaction of MAPK pathway components with LAMTOR2, 3 and MORG1 facilitates pathway activation in response to varied stimuli, resulting in the phosphorylation of MAP2K and MAPK proteins at conserved sites in their activation loops (Schaeffer et al, 1998; Teis et al, 2002; Teis et al, 2006; Vomastek et al, 2004; Sharma et al, 2005; reviewed in Matallanas et al, 2011).

Preceded by: WDR83:LAMTOR2:LAMTOR3 binds MAPK components

Literature references

Teis, D., Huber, LA., Wunderlich, W. (2002). Localization of the MP1-MAPK scaffold complex to endosomes is mediated by p14 and required for signal transduction. *Dev. Cell, 3*, 803-14. ↗

Sharma, C., Eblen, ST., Weber, MJ., Catling, AD., Tarcsafalvi, A., Vomastek, T. et al. (2005). MEK partner 1 (MP1): regulation of oligomerization in MAP kinase signaling. *J. Cell. Biochem., 94*, 708-19. ↗

Teis, D., Kurzbauer, R., Villunger, A., de Araujo, ME., Geley, S., Erlacher, M. et al. (2006). p14-MP1-MEK1 signaling regulates endosomal traffic and cellular proliferation during tissue homeostasis. *J. Cell Biol., 175*, 861-8. ↗

Eblen, ST., Weber, MJ., Collier, LS., Catling, AD., Schaeffer, HJ., Krauss, A. (1998). MP1: a MEK binding partner that enhances enzymatic activation of the MAP kinase cascade. *Science, 281*, 1668-71. ↗

Weber, MJ., Tarcsafalvi, A., Vomastek, T., Schaeffer, HJ., Bissonette, EA., Smolkin, ME. (2004). Modular construction of a signaling scaffold: MORG1 interacts with components of the ERK cascade and links ERK signaling to specific agonists. *Proc. Natl. Acad. Sci. U.S.A., 101*, 6981-6. ↗

Editions

2015-02-10	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

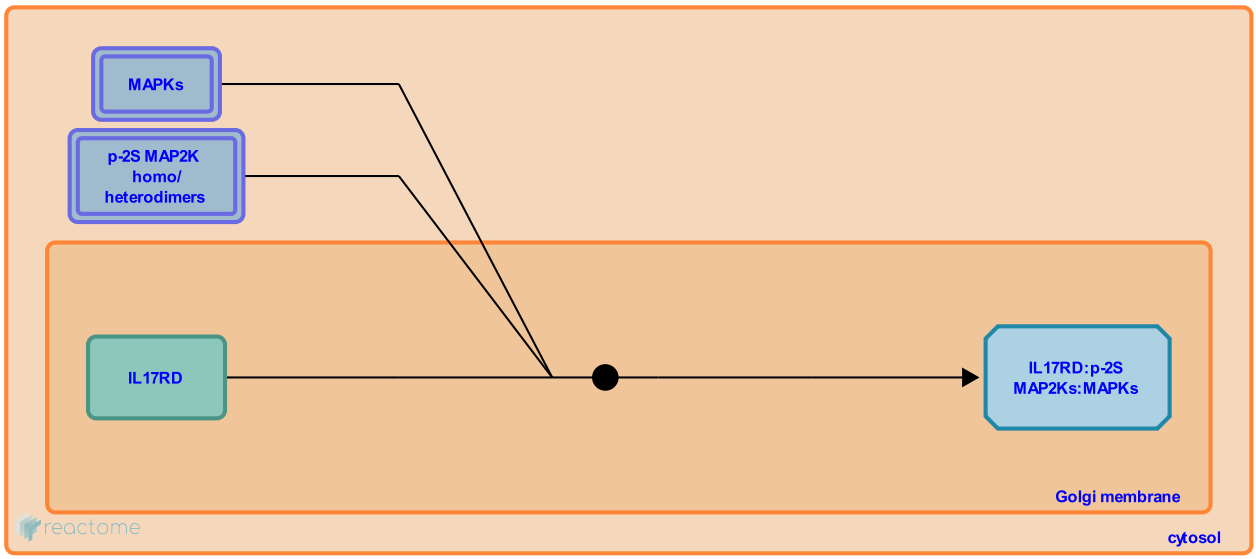
IL17RD binds p-2S MAP2Ks and MAPKs ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5674366

Type: binding

Compartments: Golgi membrane



IL17RD, also known as SEF (similar expression to FGF), was identified as a negative regulator of nuclear MAPK signaling (Tsang et al, 2002; Furthauer et al, 2002). IL17RD is a spatial regulator of MAPK signaling that binds activated MAP2K dimers at the Golgi membrane and prevents the dissociation and translocation of phosphorylated MAPK into the nucleus. In this way, IL17RD restricts activation of nuclear MAPK targets while not affecting activation of cytosolic ones (Torii et al, 2004; reviewed in Phillips, 2004; Matallanas et al, 2011).

Preceded by: Dissociation of RAS:RAF complex

Followed by: MAP2Ks phosphorylate MAPK at the Golgi membrane

Literature references

Dawid, IB., Kudoh, T., Tsang, M., Friesel, R. (2002). Identification of Sef, a novel modulator of FGF signalling. *Nat. Cell Biol., 4*, 165-9. ↗

Philips, MR. (2004). Sef: a MEK/ERK catcher on the Golgi. *Mol. Cell, 15*, 168-9. ↗

Ang, SL., Lin, W., Fürthauer, M., Thisse, B., Thisse, C. (2002). Sef is a feedback-induced antagonist of Ras/MAPK-mediated FGF signalling. *Nat. Cell Biol., 4*, 170-4. ↗

Maekawa, M., Kusakabe, M., Yamamoto, T., Nishida, E., Torii, S. (2004). Sef is a spatial regulator for Ras/MAP kinase signaling. *Dev Cell, 7*, 33-44. ↗

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

2015-02-11	Authored	Rothfels, K.
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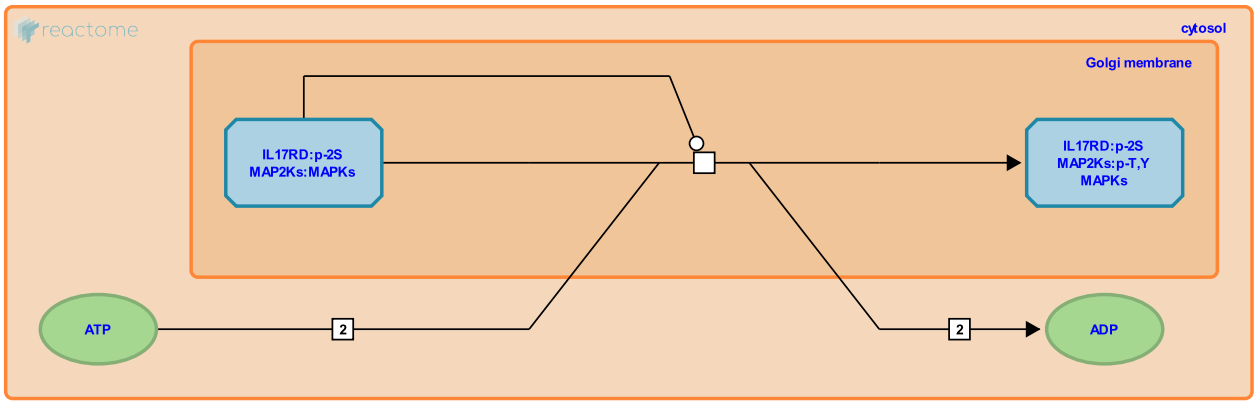
MAP2Ks phosphorylate MAPK at the Golgi membrane ↗

Location: MAP2K and MAPK activation

Stable identifier: R-HSA-5674373

Type: transition

Compartments: Golgi membrane



Activated MAP2Ks in complex with IL17RD phosphorylate MAPKs at the Golgi membrane. IL17RD prevents the dissociation of phosphorylated MAPK from the complex at the Golgi as assessed by coimmunoprecipitation, preventing MAPK nuclear translocation and activation of nuclear targets (Torii et al, 2004; reviewed in Philips, 2004; Brown and Sacks, 2009).

Preceded by: IL17RD binds p-2S MAP2Ks and MAPKs

Literature references

Brown, MD., Sacks, DB. (2009). Protein scaffolds in MAP kinase signalling. *Cell. Signal., 21*, 462-9. ↗

Philips, MR. (2004). Sef: a MEK/ERK catcher on the Golgi. *Mol. Cell, 15*, 168-9. ↗

Maekawa, M., Kusakabe, M., Yamamoto, T., Nishida, E., Torii, S. (2004). Sef is a spatial regulator for Ras/MAP kinase signaling. *Dev Cell, 7*, 33-44. ↗

Editions

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