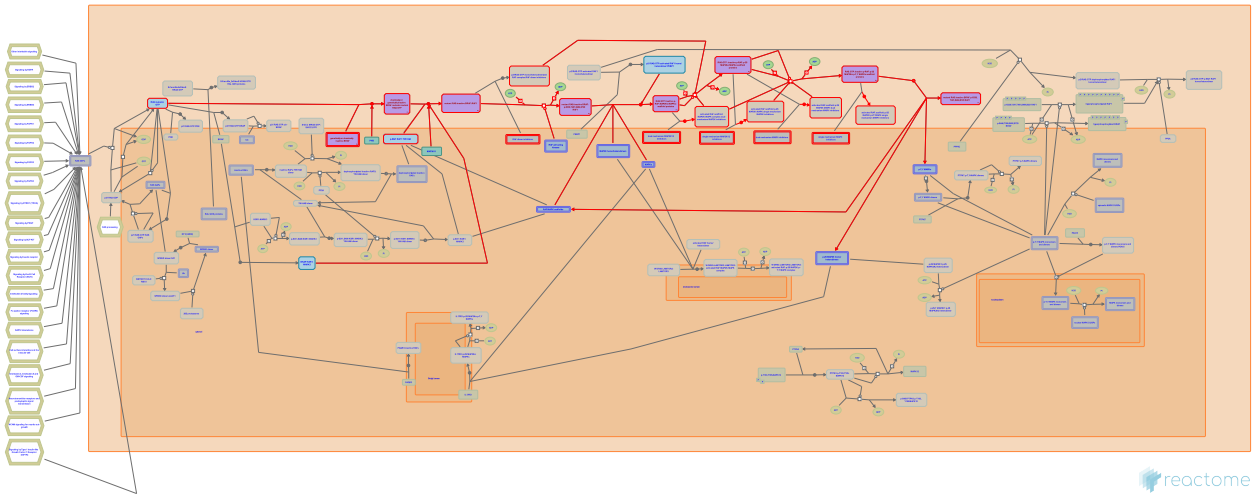
Paradoxical activation of RAF signaling by kinase inactive BRAF



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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. ↗

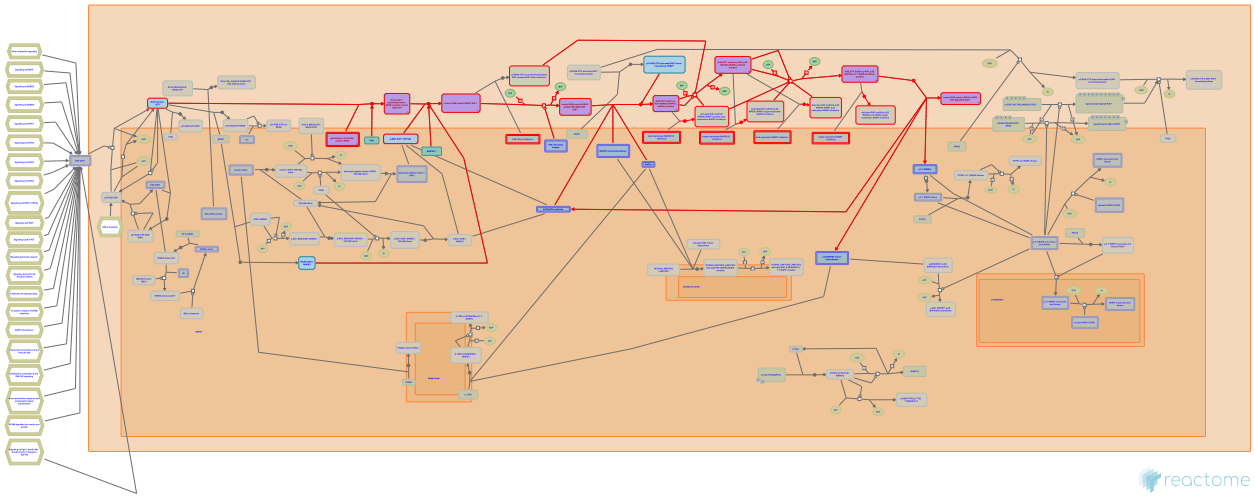
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Paradoxical activation of RAF signaling by kinase inactive BRAF ↗

Stable identifier: R-HSA-6802955

Diseases: cancer



While BRAF-specific inhibitors inhibit MAPK/ERK activation in the presence of the BRAF V600E mutant, paradoxical activation of ERK signaling has been observed after treatment of cells with inhibitor in the presence of WT BRAF (Wan et al, 2004; Garnett et al, 2005; Heidorn et al, 2010; Hazivassiliou et al, 2010; Poulikakos et al, 2010). This paradoxical ERK activation is also seen in cells expressing kinase-dead or impaired versions of BRAF such as D594V, which occur with low frequency in some cancers (Wan et al, 2004; Heidorn et al, 2010). Unlike BRAF V600E, which occurs exclusively of activating RAS mutations, kinase-impaired versions of BRAF are coincident with RAS mutations in human cancers, and indeed, paradoxical activation of ERK signaling in the presence of inactive BRAF is enhanced in the presence of oncogenic RAS (Heidorn et al, 2010; reviewed in Holderfield et al, 2014). Although the details remain to be worked out, paradoxical ERK activation in the presence of inactive BRAF appears to rely on enhanced dimerization with and transactivation of CRAF (Heidorn et al, 2010; Hazivassiliou et al, 2010; Poulikakos et al, 2010; Roring et al, 2012; Rajakulendran et al, 2009; Holderfield et al, 2013; Freeman et al, 2013; reviewed in Roskoski, 2010; Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015). RAF inhibitors can promote association of RAF-RAS interaction and enhanced RAF dimerization through disruption of intramolecular interactions between the kinase domain and its N-terminal regulatory region. Moreover, specific BRAF inhibitors can only occupy one protomer within the transcactivated BRAF dimer due to negative co-operativity leading to paradoxical ERK activation. (Karoulia et al, 2016; Jin et al, 2017, reviewed in Karoulia et al, 2017).

Literature references

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Hatzivassiliou, G., Belvin, M., Stokoe, D., Ludlam, MJ., Alvarado, R., Morales, T. et al. (2010). RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature, 464*, 431-5. ↗

Stuart, DD., Wallroth, M., Hekmat-Nejad, M., McCormick, F., Chan, J., Tandeske, L. et al. (2013). RAF inhibitors activate the MAPK pathway by relieving inhibitory autophosphorylation. *Cancer Cell, 23*, 594-602. ↗

Poulikakos, PI., Gavathiotis, E., Wu, Y., Fagin, JA., Bollard, J., Ahmed, TA. et al. (2016). An Integrated Model of RAF Inhibitor Action Predicts Inhibitor Activity against Oncogenic BRAF Signaling. *Cancer Cell, 30*, 485-498. ↗

Fiala, GJ., Herr, R., Röring, M., Heilmann, K., Schamel, WW., Saunders, DN. et al. (2012). Distinct requirement for an intact dimer interface in wild-type, V600E and kinase-dead B-Raf signalling. *EMBO J., 31*, 2629-47. ↗

Editions

2015-05-18	Edited	Rothfels, K.
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2016-08-05	Reviewed	Stephens, RM.

Inactive BRAF mutants bind mutant RAS:GTP ↗

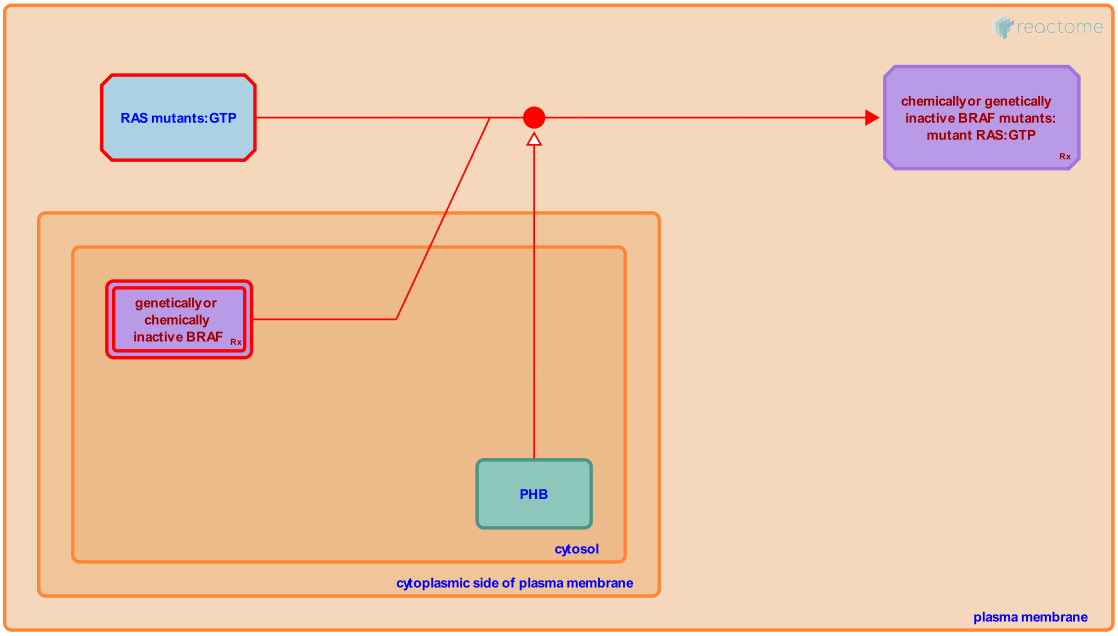
Location: Paradoxical activation of RAF signaling by kinase inactive BRAF

Stable identifier: R-HSA-6802937

Type: binding

Compartments: plasma membrane

Diseases: cancer



The paradoxical activation of ERK signaling downstream of kinase-dead or inhibited forms of BRAF appears to result from enhanced dimerization with RAF1/CRAF (Wan et al, 2004; Poulikakos et al, 2010; Heidorn et al, 2010; Hatzivassilliou et al, 2010; Freeman et al, 2013). The propensity to dimerize may be promoted by conformational changes in the BRAF monomer as a result of mutation or inhibitor binding (reviewed in Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015).

Followed by: Inactive BRAF mutants:mutant RAS:GTP bind RAF1

Literature references

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Fiala, GJ., Herr, R., Röring, M., Heilmann, K., Schamel, WW., Saunders, DN. et al. (2012). Distinct requirement for an intact dimer interface in wild-type, V600E and kinase-dead B-Raf signalling. *EMBO J., 31*, 2629-47. ↗

Freeman, AK., Ritt, DA., Morrison, DK. (2013). Effects of Raf dimerization and its inhibition on normal and disease-associated Raf signaling. *Mol. Cell, 49*, 751-8. ↗

Hatzivassiliou, G., Belvin, M., Stokoe, D., Ludlam, MJ., Alvarado, R., Morales, T. et al. (2010). RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature, 464*, 431-5. ↗

Reis-Filho, JS., Heidorn, SJ., Springer, CJ., Pritchard, C., Nourry, A., Milagre, C. et al. (2010). Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell, 140*, 209-21. ↗

Editions

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Inactive BRAF mutants:mutant RAS:GTP bind RAF1 ↗

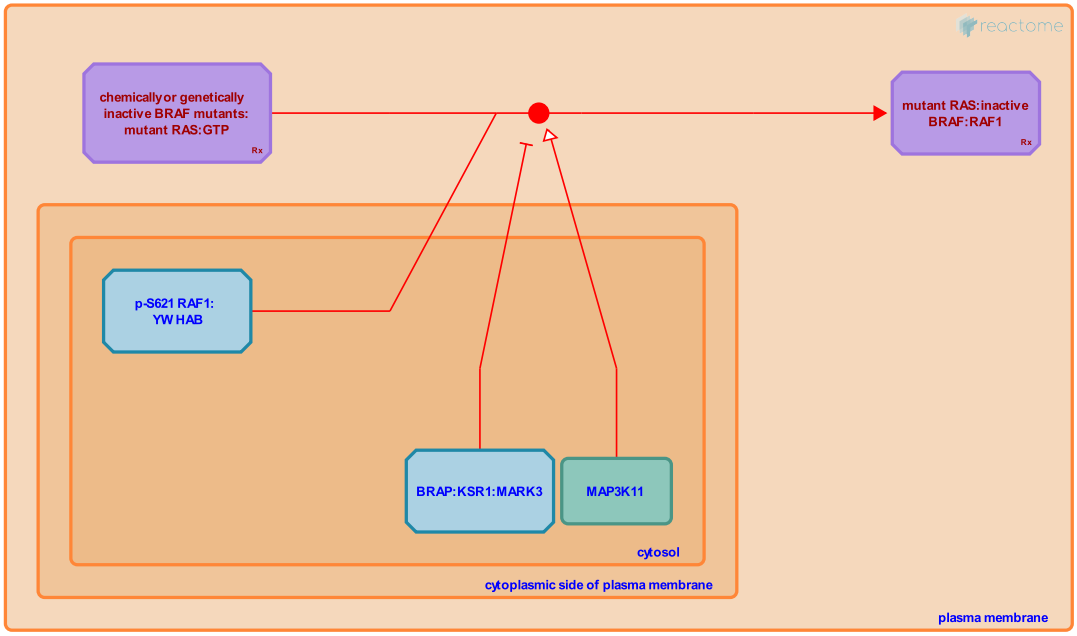
Location: Paradoxical activation of RAF signaling by kinase inactive BRAF

Stable identifier: R-HSA-8936731

Type: binding

Compartments: plasma membrane

Diseases: cancer



The paradoxical activation of ERK signaling downstream of kinase-dead or inhibited forms of BRAF appears to result from enhanced dimerization with RAF1/CRAF (Wan et al, 2004; Poulikakos et al, 2010; Heidorn et al, 2010; Hatzivassilliou et al, 2010; Freeman et al, 2013). The propensity to dimerize may be promoted by conformational changes in the BRAF monomer as a result of mutation or inhibitor binding (reviewed in Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015).

Preceded by: Inactive BRAF mutants bind mutant RAS:GTP

Followed by: RAF is paradoxically phosphorylated downstream of kinase-inactive RAF

Literature references

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Fiala, GJ., Herr, R., Röring, M., Heilmann, K., Schamel, WW., Saunders, DN. et al. (2012). Distinct requirement for an intact dimer interface in wild-type, V600E and kinase-dead B-Raf signalling. *EMBO J., 31*, 2629-47. ↗

Freeman, AK., Ritt, DA., Morrison, DK. (2013). Effects of Raf dimerization and its inhibition on normal and disease-associated Raf signaling. *Mol. Cell, 49*, 751-8. ↗

Hatzivassiliou, G., Belvin, M., Stokoe, D., Ludlam, MJ., Alvarado, R., Morales, T. et al. (2010). RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature, 464*, 431-5. ↗

Reis-Filho, JS., Heidorn, SJ., Springer, CJ., Pritchard, C., Nourry, A., Milagre, C. et al. (2010). Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell, 140*, 209-21. ↗

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RAF is paradoxically phosphorylated downstream of kinase-inactive RAF ↗

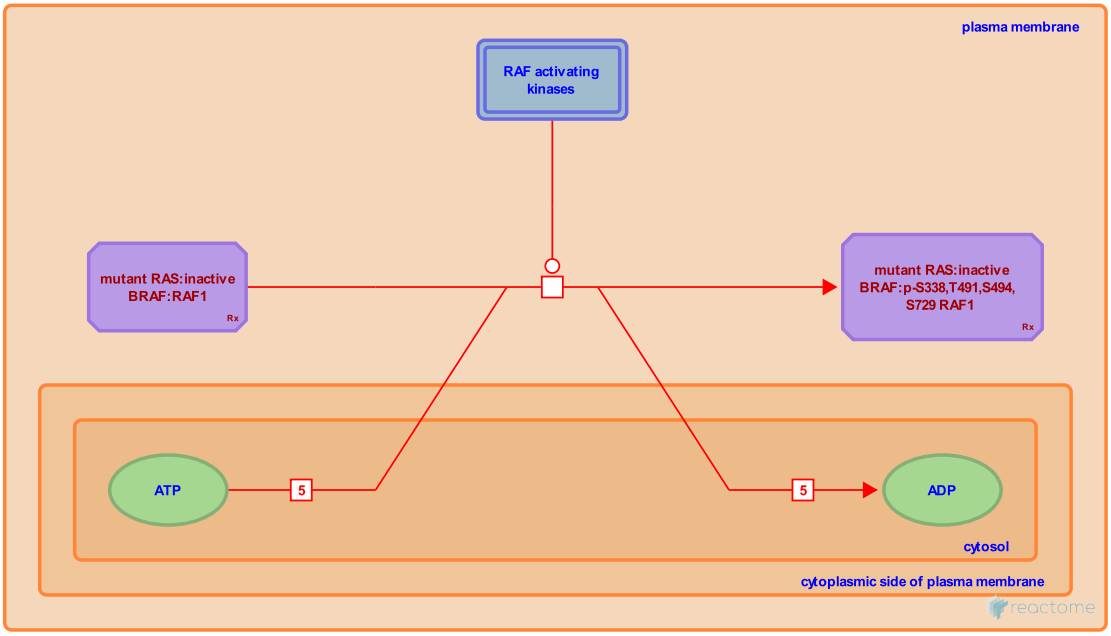
Location: Paradoxical activation of RAF signaling by kinase inactive BRAF

Stable identifier: R-HSA-6802941

Type: transition

Compartments: plasma membrane

Diseases: cancer



The enhanced dimerization of inhibited or kinase dead versions of BRAF to RAF1/CRAF stimulates the phosphorylation and transactivation of RAF1 (Wan et al, 2004; Garnett et al, 2005; Heidorn et al, 2010; Poulikakos et al, 2010; Hatzivassiliou et al, 2010; reviewed in Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015). Other evidence suggests that paradoxical activation of RAF1 by inhibited or inactive BRAF may result from relief of an inhibitory CRAF autophosphorylation event (Holderfield et al, 2013; reviewed in Holderfield, 2014).

Preceded by: Inactive BRAF mutants:mutant RAS:GTP bind RAF1

Followed by: RAS:GTP:p-RAF complexes paradoxically bind MAP2Ks and MAPKs

Literature references

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Stuart, DD., Wallroth, M., Hekmat-Nejad, M., McCormick, F., Chan, J., Tandeske, L. et al. (2013). RAF inhibitors activate the MAPK pathway by relieving inhibitory autophosphorylation. *Cancer Cell, 23*, 594-602. ↗

McCormick, F., Deuker, MM., McMahon, M., Holderfield, M. (2014). Targeting RAF kinases for cancer therapy: BRAF-mutated melanoma and beyond. *Nat. Rev. Cancer, 14*, 455-67. ↗

Hatzivassiliou, G., Belvin, M., Stokoe, D., Ludlam, MJ., Alvarado, R., Morales, T. et al. (2010). RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature, 464*, 431-5. ↗

Reis-Filho, JS., Heidorn, SJ., Springer, CJ., Pritchard, C., Nourry, A., Milagre, C. et al. (2010). Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell, 140*, 209-21. ↗

Editions

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2016-08-05	Reviewed	Stephens, RM.

RAS:GTP:p-RAF complexes paradoxically bind MAP2Ks and MAPKs ↗

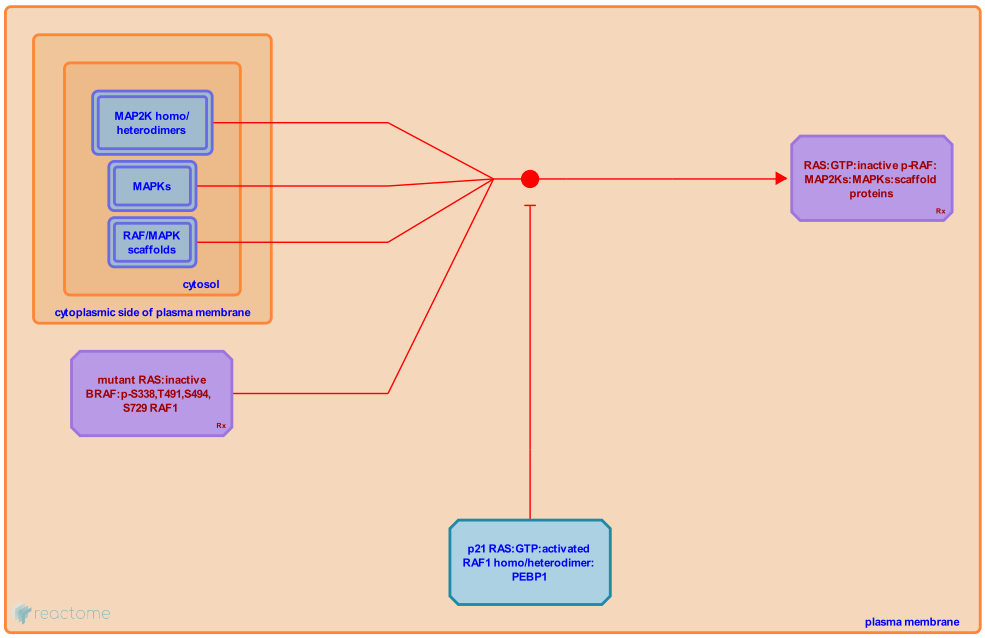
Location: Paradoxical activation of RAF signaling by kinase inactive BRAF

Stable identifier: R-HSA-6802942

Type: binding

Compartments: plasma membrane

Diseases: cancer



Dimerization of kinase-dead or inhibited versions of BRAF to RAF1/CRAF leads to the recruitment and phosphorylation of MAP2Ks and MAPKs (Wan et al, 2004; Garnett et al, 2005; Heidorn et al, 2010; Poulikakos et al, 2010; Hatzivassiliou et al, 2010; reviewed in Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015). Although the interactions haven't been studied in detail, these disease pathways are presumed to recruit MAP2Ks and MAPKs in a scaffold-dependent manner similar to WT (reviewed in Matallanas et al, 2011).

Preceded by: RAF is paradoxically phosphorylated downstream of kinase-inactive RAF

Followed by: RAS:GTP:inactive p-RAF complexes phosphorylate MAP2Ks

Literature references

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Hatzivassiliou, G., Belvin, M., Stokoe, D., Ludlam, MJ., Alvarado, R., Morales, T. et al. (2010). RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature, 464*, 431-5. ↗

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Garnett, MJ., Barford, D., Paterson, H., Rana, S., Marais, R. (2005). Wild-type and mutant B-RAF activate C-RAF through distinct mechanisms involving heterodimerization. *Mol. Cell, 20*, 963-9. ↗

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

Editions

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RAS:GTP:inactive p-RAF complexes phosphorylate MAP2Ks ↗

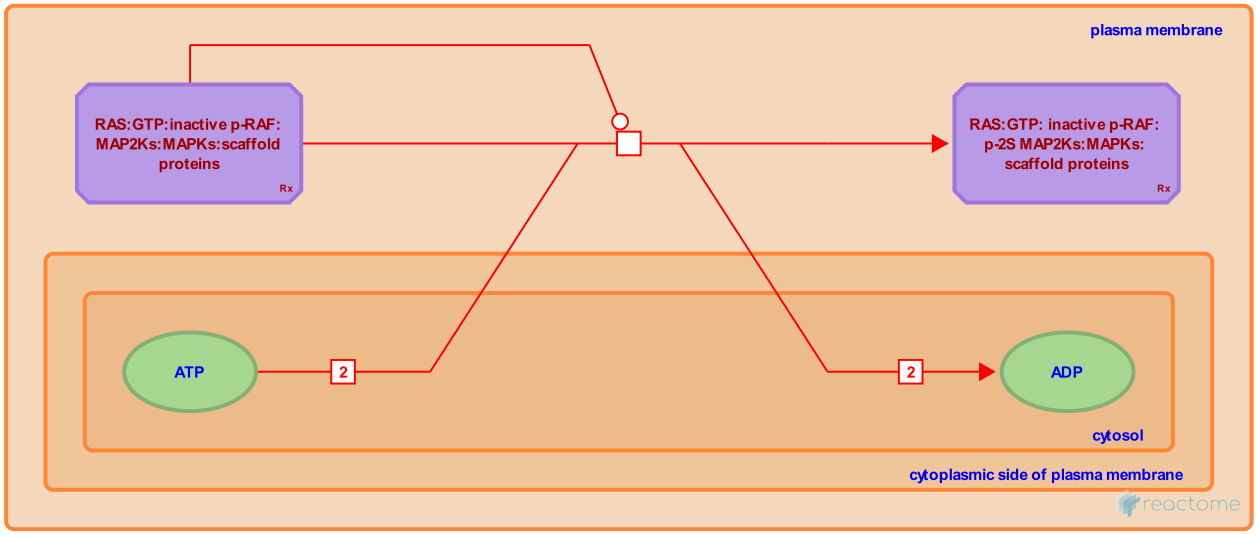
Location: Paradoxical activation of RAF signaling by kinase inactive BRAF

Stable identifier: R-HSA-6802943

Type: transition

Compartments: plasma membrane

Diseases: cancer



As in the WT pathway, activation of ERK signaling downstream of kinase-dead or inhibited forms of BRAF depends on phosphorylation of two serine residues in the activation loop of the MAP2K proteins (Wan et al, 2004; Garnett et al, 2005; Heidorn et al, 2010; Poulikakos et al, 2010; Hatzivassiliou et al, 2010; reviewed in Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015).

Preceded by: RAS:GTP:p-RAF complexes paradoxically bind MAP2Ks and MAPKs

Literature references

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Hatzivassiliou, G., Belvin, M., Stokoe, D., Ludlam, MJ., Alvarado, R., Morales, T. et al. (2010). RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature, 464*, 431-5. ↗

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Garnett, MJ., Barford, D., Paterson, H., Rana, S., Marais, R. (2005). Wild-type and mutant B-RAF activate C-RAF through distinct mechanisms involving heterodimerization. *Mol. Cell, 20*, 963-9. ↗

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

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Activated MAP2Ks phosphorylate MAPKs downstream of inactive BRAF mutants ↗

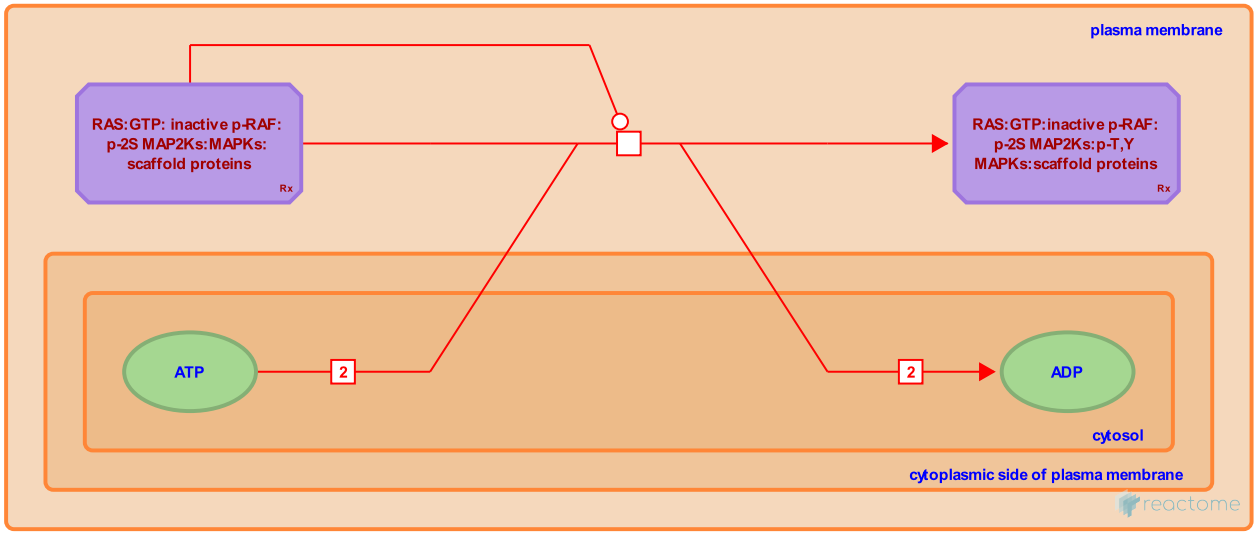
Location: Paradoxical activation of RAF signaling by kinase inactive BRAF

Stable identifier: R-HSA-6802918

Type: transition

Compartments: plasma membrane

Diseases: cancer



Downstream of kinase-dead or inhibited forms of BRAF, activated MAP2K phosphorylates MAPK on threonine and tyrosine residues in the activation loop (Wan et al, 2004; Garnett et al, 2005; Heidorn et al, 2010; Poulikakos et al, 2010; Hatzivassilliou et al, 2010; reviewed in Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015).

Literature references

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Hatzivassiliou, G., Belvin, M., Stokoe, D., Ludlam, MJ., Alvarado, R., Morales, T. et al. (2010). RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature, 464*, 431-5. ↗

Reis-Filho, JS., Heidorn, SJ., Springer, CJ., Pritchard, C., Nourry, A., Milagre, C. et al. (2010). Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell, 140*, 209-21. ↗

Garnett, MJ., Barford, D., Paterson, H., Rana, S., Marais, R. (2005). Wild-type and mutant B-RAF activate C-RAF through distinct mechanisms involving heterodimerization. *Mol. Cell, 20*, 963-9. ↗

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

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Dissociation of paradoxically activated RAS:BRAF complexes ↗

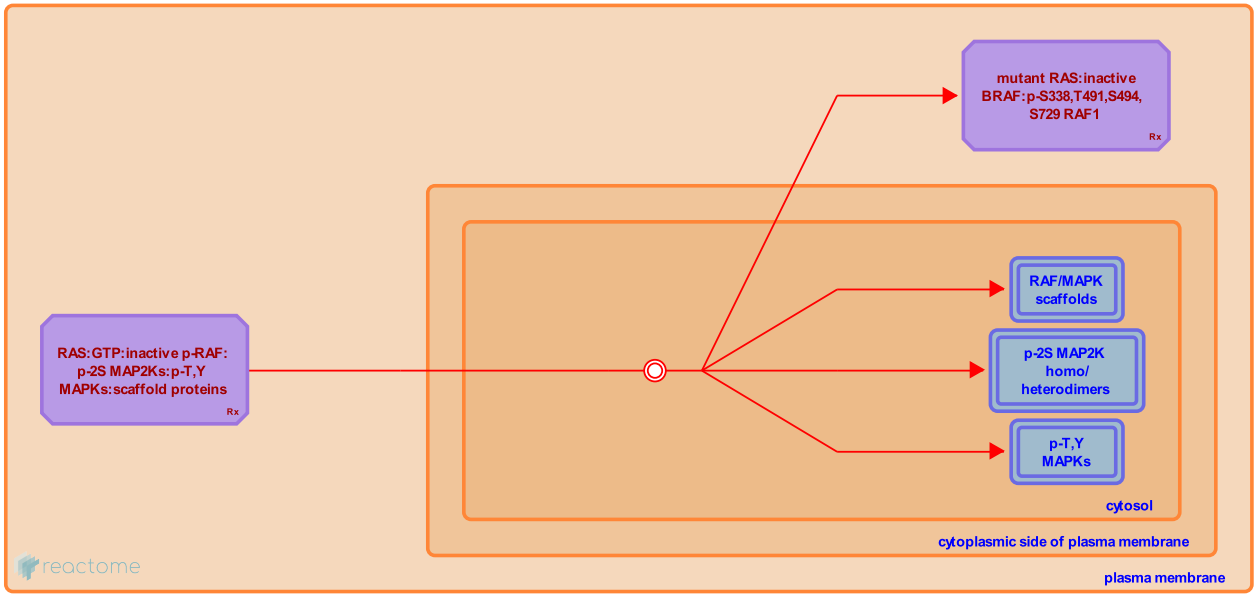
Location: Paradoxical activation of RAF signaling by kinase inactive BRAF

Stable identifier: R-HSA-6803234

Type: dissociation

Compartments: cytosol

Diseases: cancer



After phosphorylation by MAP2Ks, the scaffolded kinase complex assembled by kinase dead or inhibited BRAF mutants dissociates, as is the case for WT complexes (reviewed in Lavoie and Therrien et al, 2015).

Literature references

Lavoie, H., Therrien, M. (2015). Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol., 16*, 281-98. ↗

Editions

2015-08-10	Authored, Edited	Rothfels, K.
2016-08-05	Reviewed	Stephens, RM.

Table of Contents