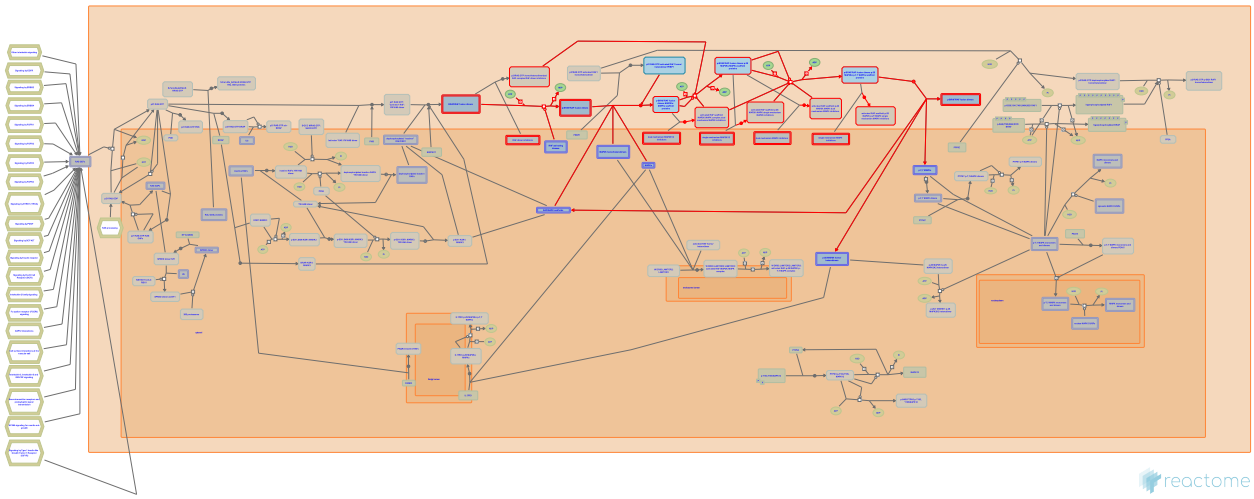
Signaling by BRAF and RAF1 fusions



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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).

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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. ↗

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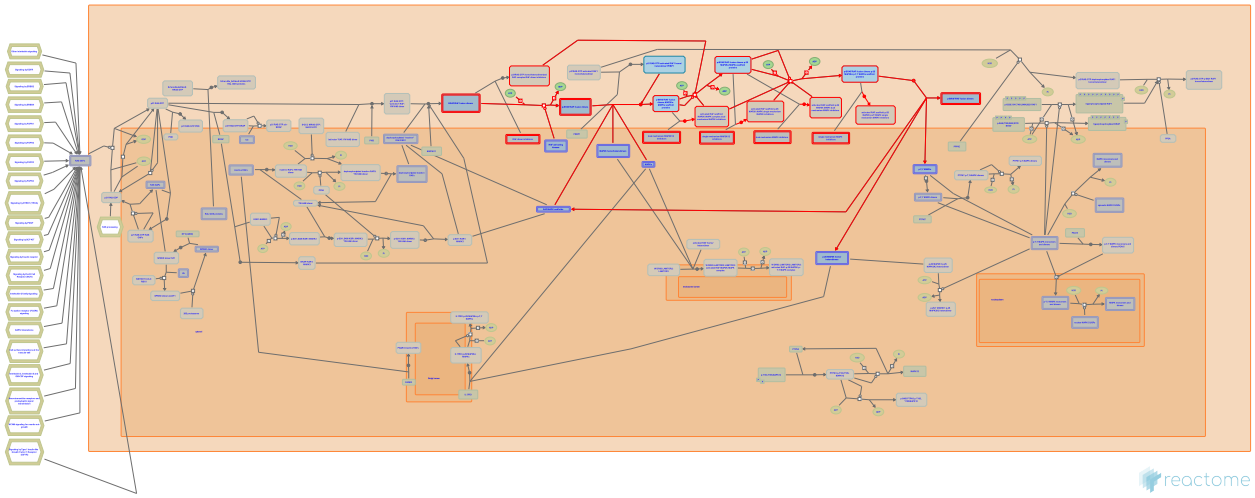
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Signaling by BRAF and RAF1 fusions ↗

Stable identifier: R-HSA-6802952

Diseases: cancer



In addition to the more prevalent point mutations, BRAF and RAF1 are also subject to activation as a result of translocation events that yield truncated or fusion products (Jones et al, 2008; Cin et al, 2011; Palanisamy et al, 2010; Ciampi et al, 2005; Stransky et al, 2014; Hutchinson et al, 2013; Zhang et al, 2013; Lee et al, 2012; Ricarte-Filho et al, 2013; reviewed in Lavoie and Therrien et al, 2015). In general these events put the C-terminal kinase domain of BRAF or RAF1 downstream of an N-terminal sequence provided by a partner protein. This removes the N-terminal region of the RAF protein, relieving the autoinhibition imposed by this region of the protein. In addition, some but not all of the fusion partner proteins have been shown to contain coiled-coil or other dimerization domains. Taken together, the fusion proteins are thought to dimerize constitutively and activate downstream signaling (Jones et al, 2008; Lee et al, 2012; Hutchinson et al, 2013; Ciampi et al, 2005; Cin et al, 2011; Stransky et al, 2014).

Literature references

Lu, C., Dooling, DJ., Qaddoumi, I., Parker, M., Ellison, DW., Rusch, M. et al. (2013). Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat. Genet., 45*, 602-12. ↗

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Editions

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

BRAF and RAF fusion mutant dimers are phosphorylated ↗

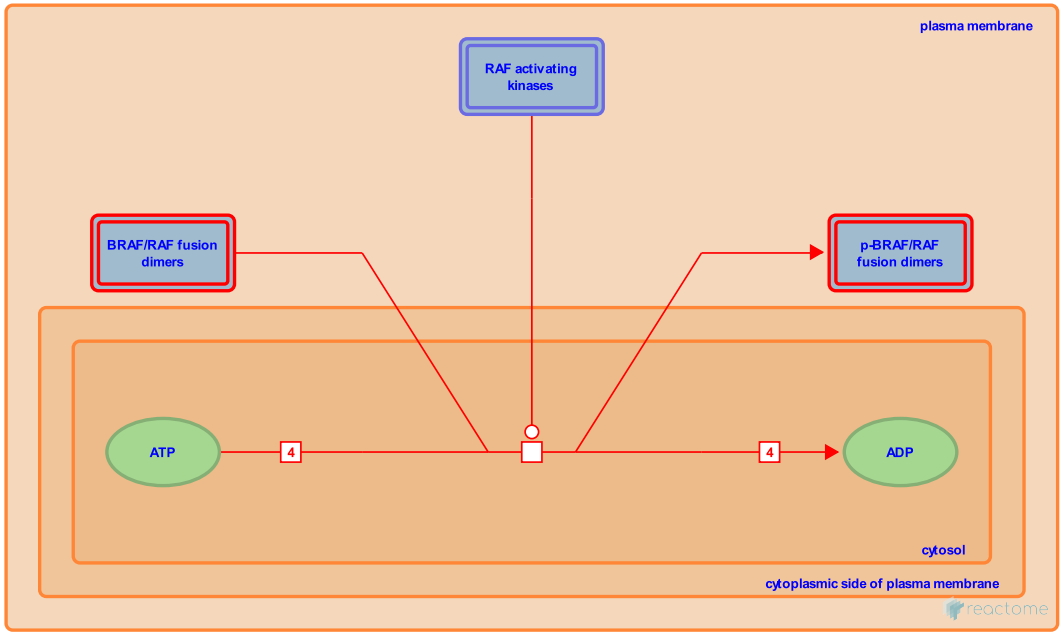
Location: Signaling by BRAF and RAF1 fusions

Stable identifier: R-HSA-6802927

Type: transition

Compartments: cytosol

Diseases: cancer



Fusion mutants of BRAF and RAF1 are believed to form constitutive dimers and activate downstream signaling independent of RAS and external stimuli (Jones et al, 2008; Cin et al, 2011; Palanisamy et al, 2010; Ciampi et al, 2005; Stransky et al, 2014; Hutchinson et al, 2013; Zhang et al, 2013; Lee et al, 2012; Ricarte-Filho et al, 2013; reviewed in Lavoie and Therrien et al, 2015). The RAF portion of the fusion mutants may undergo phosphorylation of the N-region and activation loops similar to WT as shown in this reaction, although this has not been studied in detail. While WT RAF phosphorylation happens in the context of a complex with with RAS, this is unlikely to be the case for the fusion mutants, as many of these proteins lack the N-terminal RAS binding domain (reviewed in Lavoie and Therrien, 2015).

Followed by: p-BRAF and RAF fusion dimers bind MAP2Ks and MAPKs

Literature references

Hutchinson, KE., Lyle, PL., Puzanov, I., Sosman, JA., Pietenpol, JA., Lehmann, BD. et al. (2013). BRAF fusions define a distinct molecular subset of melanomas with potential sensitivity to MEK inhibition. *Clin. Cancer Res., 19*, 6696-702. ↗

Kerler, R., Fagin, JA., Rabes, HM., Nikiforov, YE., Knauf, JA., Gandhi, M. et al. (2005). Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. *J. Clin. Invest., 115*, 94-101. ↗

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

Herr, R., Scheurlen, W., Jabado, N., Jacob, K., Gnekow, A., Collins, VP. et al. (2011). Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. *Acta Neuropathol., 121*, 763-74. ↗

Shankar, S., Siddiqui, J., Kuefer, R., Chen, YB., Greenson, JK., Lafargue, CJ. et al. (2010). Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat. Med., 16*, 793-8. ↗

Editions

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p-BRAF and RAF fusion dimers bind MAP2Ks and MAPKs ↗

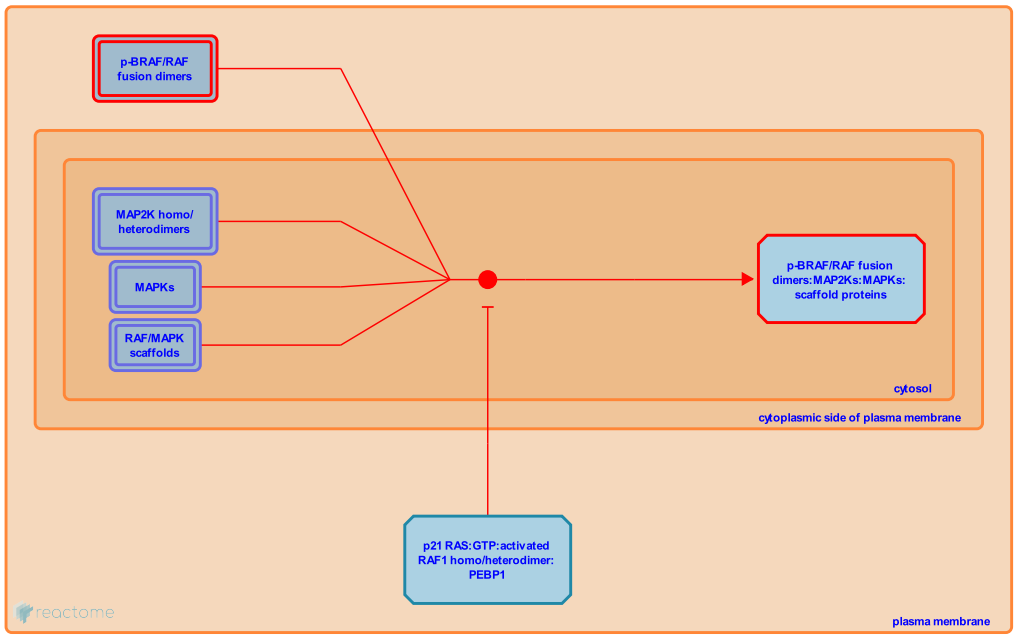
Location: Signaling by BRAF and RAF1 fusions

Stable identifier: R-HSA-6802934

Type: binding

Compartments: cytosol

Diseases: cancer



BRAF and RAF fusion proteins expressed in cancer constitutively activate downstream signaling and promote cellular transformation (Jones et al, 2008; Cin et al, 2011; Palanisamy et al, 2010; Ciampi et al, 2005; Stransky et al, 2014; Hutchinson et al, 2013; Zhang et al, 2013; Lee et al, 2012; Ricarte-Filho et al, 2013; reviewed in Lavoie and Therrien et al, 2015). Recruitment of MAP2Ks and MAPKs to the fusion dimers may occur in conjunction with scaffold proteins as is the case for WT RAF dimers, however this has not been studied in detail.

Preceded by: BRAF and RAF fusion mutant dimers are phosphorylated

Followed by: p-BRAF and RAF fusion dimers phosphorylate MAP2Ks

Literature references

Hutchinson, KE., Lyle, PL., Puzanov, I., Sosman, JA., Pietenpol, JA., Lehmann, BD. et al. (2013). BRAF fusions define a distinct molecular subset of melanomas with potential sensitivity to MEK inhibition. *Clin. Cancer Res., 19*, 6696-702. ↗

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

Herr, R., Scheurlen, W., Jabado, N., Jacob, K., Gnekow, A., Collins, VP. et al. (2011). Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. *Acta Neuropathol., 121*, 763-74. ↗

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p-BRAF and RAF fusion dimers phosphorylate MAP2Ks ↗

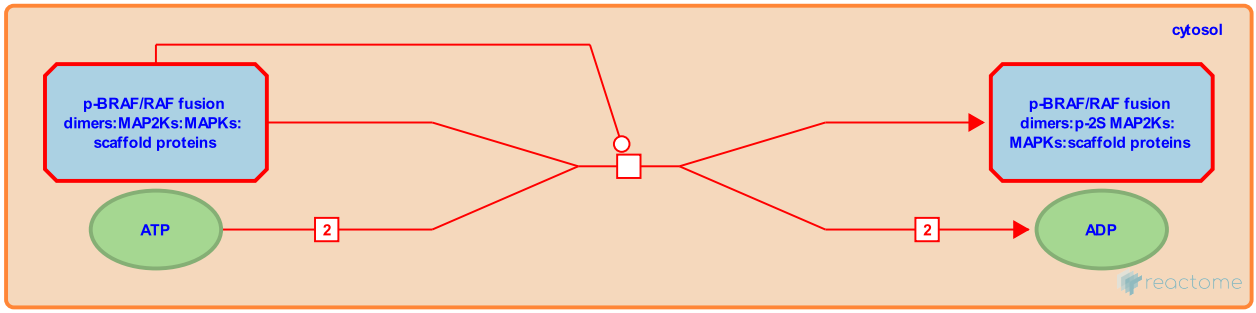
Location: Signaling by BRAF and RAF1 fusions

Stable identifier: R-HSA-6802933

Type: transition

Compartments: cytosol

Diseases: cancer



BRAF and RAF fusion dimers constitutively phosphorylate MAP2Ks (Jones et al, 2008; Cin et al, 2011; Palanisamy et al, 2010; Ciampi et al, 2005; Stransky et al, 2014; Hutchinson et al, 2013; Zhang et al, 2013; Lee et al, 2012; Ricarte-Filho et al, 2013; reviewed in Lavoie and Therrien et al, 2015).

Preceded by: p-BRAF and RAF fusion dimers bind MAP2Ks and MAPKs

Followed by: MAPKs are phosphorylated downstream of BRAF and RAF fusion dimers

Literature references

Hutchinson, KE., Lyle, PL., Puzanov, I., Sosman, JA., Pietenpol, JA., Lehmann, BD. et al. (2013). BRAF fusions define a distinct molecular subset of melanomas with potential sensitivity to MEK inhibition. *Clin. Cancer Res., 19*, 6696-702. ↗

Kerler, R., Fagin, JA., Rabes, HM., Nikiforov, YE., Knauf, JA., Gandhi, M. et al. (2005). Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. *J. Clin. Invest., 115*, 94-101. ↗

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

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Shankar, S., Siddiqui, J., Kuefer, R., Chen, YB., Greenson, JK., Lafargue, CJ. et al. (2010). Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat. Med., 16*, 793-8. ↗

Editions

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MAPKs are phosphorylated downstream of BRAF and RAF fusion dimers ↗

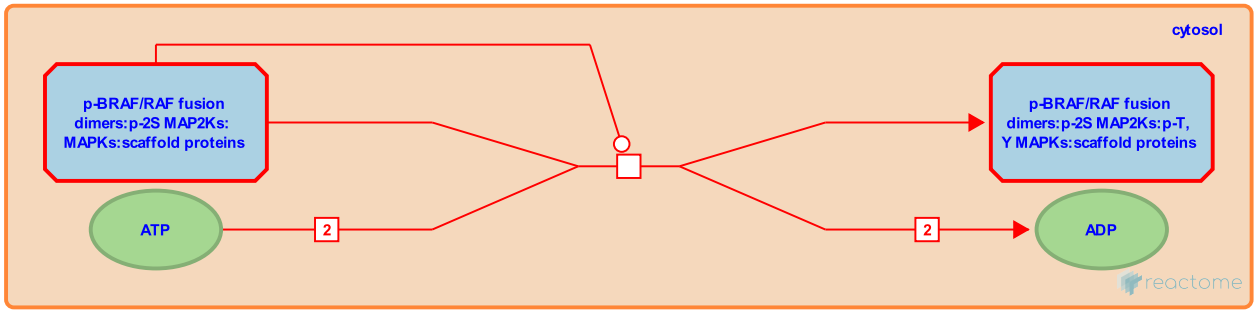
Location: Signaling by BRAF and RAF1 fusions

Stable identifier: R-HSA-6802935

Type: transition

Compartments: cytosol

Diseases: cancer



MAPKs are phosphorylated downstream of constitutively active BRAF and RAF fusion proteins (Jones et al, 2008; Cin et al, 2011; Palanisamy et al, 2010; Ciampi et al, 2005; Stransky et al, 2014; Hutchinson et al, 2013; Zhang et al, 2013; Lee et al, 2012; Ricarte-Filho et al, 2013; reviewed in Lavoie and Therrien et al, 2015).

Preceded by: p-BRAF and RAF fusion dimers phosphorylate MAP2Ks

Followed by: Dissociation of BRAF/RAF fusion complex

Literature references

Hutchinson, KE., Lyle, PL., Puzanov, I., Sosman, JA., Pietenpol, JA., Lehmann, BD. et al. (2013). BRAF fusions define a distinct molecular subset of melanomas with potential sensitivity to MEK inhibition. *Clin. Cancer Res., 19*, 6696-702. ↗

Kerler, R., Fagin, JA., Rabes, HM., Nikiforov, YE., Knauf, JA., Gandhi, M. et al. (2005). Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. *J. Clin. Invest., 115*, 94-101. ↗

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Dissociation of BRAF/RAF fusion complex ↗

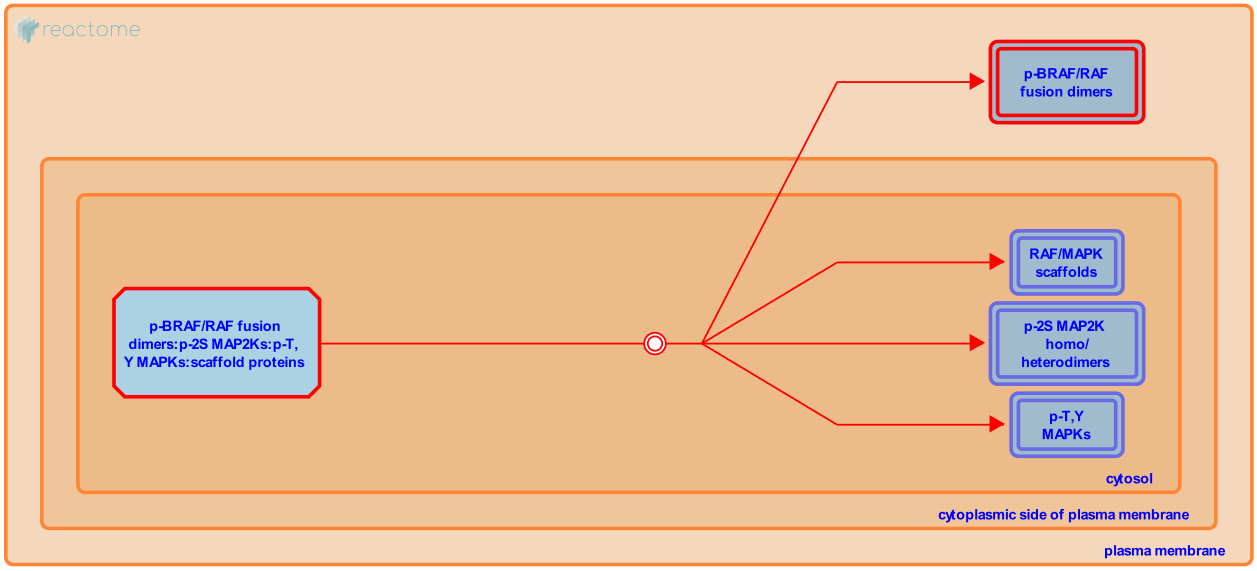
Location: Signaling by BRAF and RAF1 fusions

Stable identifier: R-HSA-6802932

Type: dissociation

Compartments: cytosol

Diseases: cancer



After phosphorylation by MAP2Ks, the scaffolded kinase complex assembled by BRAF and RAF fusion dimers presumably dissociates, as is the case for WT complexes (Jones et al, 2008; Cin et al, 2011; Palanisamy et al, 2010; Ciampi et al, 2005; Stransky et al, 2014; Hutchinson et al, 2013; Zhang et al, 2013; Lee et al, 2012; Ricarte-Filho et al, 2013; reviewed in Lavoie and Therrien et al, 2015).

Preceded by: MAPKs are phosphorylated downstream of BRAF and RAF fusion dimers

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