

BRAF and RAF fusion mutant dimers are phosphorylated

Rothfels, K., Stephens, RM.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of <u>Creative Commons Attribution 4.0 International (CC BY 4.0)</u> <u>License</u>. For more information see our <u>license</u>.

18/05/2024

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. 7
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. A
- 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. *オ*

This document contains 1 reaction (see Table of Contents)

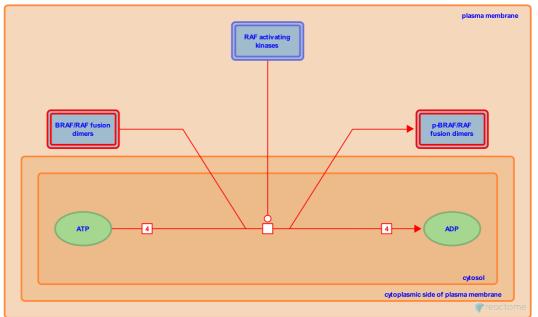
BRAF and RAF fusion mutant dimers are phosphorylated **7**

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).

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

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