Dimerization of BRAF V600E splice variants contributes to BRAF inhibitor resistance

Rothfels, K., Stephens, RM.

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

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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.

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Literature references

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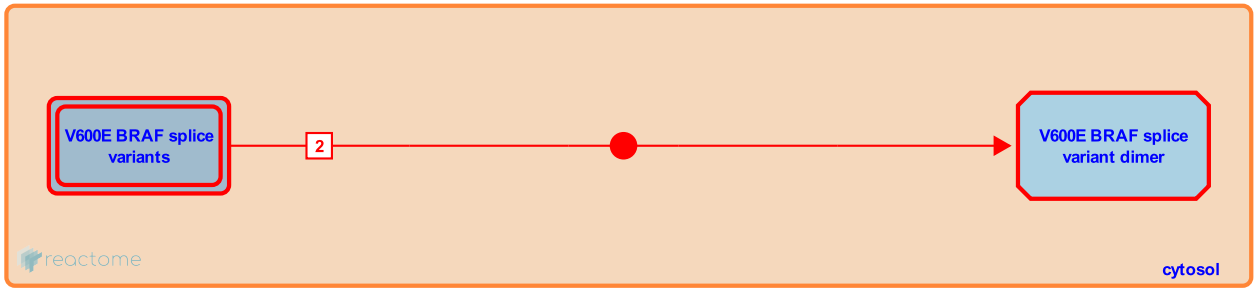
Stable identifier: R-HSA-6802930

Type: binding

Compartments: cytosol

Diseases: cancer



RAF kinase inhibitors such as vemurafenib are clinically approved for treatment of BRAF-driven melanomas. Despite initial positive response to drug treatment, however, many tumors go on to develop resistance to the RAF inhibitors (Flaherty et al, 2010; Chapman et al, 2011; Sosman et al, 2012; Solit et al, 2011; reviewed in Lito et al, 2013). One mechanism that contributes to acquired resistance to RAF inhibitors is the expression of a splice variant of V600E that lacks the N-terminal RAS-binding domain. This variant displays increased RAS-independent dimerization and increased signaling relative to the full-length V600E, consistent with the notion that it is the monomeric form of BRAF that is sensitive to inhibition. Disruption of the dimer interface in this p61-V600E splice variant restores sensitivity to inhibition (Poulikakos et al, 2011; reviewed in Lito et al, 2013).

Other mechanisms of BRAF inhibitor resistance include mutational activation of NRAS or receptor tyrosine kinases, inactivation of the GAP protein NF1, or increased expression of RAF1 or BRAF (Nazarian et al, 2010; Maertens et al, 2013; Whittaker et al, 2013; Shi et al, 2012; Montagut et al, 2008; reviewed in Chapman, 2013; Lito et al, 2013).

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Editions

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