Signaling by high-kinase activity BRAF mutants

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 Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

08/05/2020
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


Reactome database release: 72

This document contains 1 pathway and 6 reactions (see Table of Contents)
Signaling by high-kinase activity BRAF mutants

Stable identifier: R-HSA-6802948

Diseases: cancer

BRAF is mutated in about 8% of human cancers, with high prevalence in hairy cell leukemia, melanoma, papillary thyroid and ovarian carcinomas, colorectal cancer and a variety of other tumors (Davies et al, 2002; reviewed in Samatar and Poulikakos, 2014). Most BRAF mutations fall in the activation loop region of the kinase or the adjacent glycine rich region. These mutations promote increased kinase activity either by mimicking the effects of activation loop phosphorylations or by promoting the active conformation of the enzyme (Davies et al, 2002; Wan et al, 2004). Roughly 90% of BRAF mutants are represented by the single missense mutation BRAF V600E (Davies et al, 2002; Wan et al, 2004). Other highly active kinase mutants of BRAF include BRAF G469A and BRAF T599dup. G469 is in the glycine rich region of the kinase domain which plays a role in orienting ATP for catalysis, while T599 is one of the two conserved regulatory phosphorylation sites of the activation loop. Each of these mutants has highly enhanced basal kinase activities, phosphorylates MEK and ERK in vitro and in vivo and is transforming when expressed in vivo (Davies et al, 2002; Wan et al, 2004; Eisenhardt et al, 2011). Further functional characterization shows that these highly active mutants are largely resistant to disruption of the BRAF dimer interface, suggesting that they are able to act as monomers (Roring et al, 2012; Brummer et al, 2006; Freeman et al, 2013; Garnett et al, 2005). Activating BRAF mutations occur for the most part independently of RAS activating mutations, and RAS activity levels are generally low in BRAF mutant cells. Moreover, the kinase activity of these mutants is only slightly elevated by coexpression of G12V KRAS, and biological activity of the highly active BRAF mutants is independent of RAS binding (Brummer et al, 2006; Wan et al, 2004; Davies et al, 2002; Garnett et al, 2005). Although BRAF V600E is inhibited by RAF inhibitors such as vemurafenib, resistance frequently develops, in some cases mediated by the expression of a splice variant that lacks the RAS binding domain and shows elevated dimerization compared to the full length V600E mutant (Poulikakos et al, 2011; reviewed in Lito et al, 2013).

Literature references


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-08-10</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-08-05</td>
<td>Reviewed</td>
<td>Stephens, RM.</td>
</tr>
</tbody>
</table>
High kinase activity BRAF mutants bind MAP2Ks and MAPKs

**Location:** Signaling by high-kinase activity BRAF mutants

**Stable identifier:** R-HSA-6802912