Oncogenic MAPK signaling

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19/09/2021
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: 77

This document contains 11 pathways ([see Table of Contents](https://reactome.org))
Oncogenic MAPK signaling

Stable identifier: R-HSA-6802957

Diseases: cancer

The importance of the RAS/RAF/MAPK cascade in regulating cellular proliferation, differentiation and survival is highlighted by the fact that components of the pathway are mutated with high frequency in a large number of human cancers. Activating mutations in RAS are found in approximately one third of human cancers, while ~8% of tumors express an activated form of BRAF. RAS pathway activation is also achieved in a smaller subset of cancers by loss-of-function mutations in negative regulators of RAS signaling, such as the RAS GAP NF1(reviewed in Prior et al, 2012; Pylayeva-Gupta et al, 2011; Stephen et al, 2014; Lavoie and Therrien, 2015; Lito et al, 2013; Samatar and Poulikakos, 2014; Maertens and Cichowski, 2014).

Literature references


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Members of the RAS gene family were the first oncogenes to be identified, and mutations in RAS are present in ~20-30% of human cancers (reviewed in Prior et al, 2012). Mutations in the KRAS gene are the most prevalent, and are found with high frequency in colorectal cancer, non-small cell lung cancer and pancreatic cancer, among others. The reasons for the lower prevalence of HRAS and NRAS mutations in human cancers are not fully understood, but may reflect gene-specific functions as well as differential codon usage and spatio-temporal regulation (reviewed in Prior et al, 2012; Stephen et al, 2014; Pylayeva-Gupta et al, 2011). Activating RAS mutations contribute to cellular proliferation, transformation and survival by activating the MAPK signaling pathway, the AKT pathway and the RAL GDS pathway, among others (reviewed in Stephen et al, 2014; Pylayeva-Gupta et al, 2011).

Although the frequency and distribution varies between RAS genes and cancer types, the vast majority of activating RAS mutations occur at one of three residues - G12, G13 and Q61. Mutations at these sites favour the RAS:GTP bound form and yield constitutively active versions of the protein (reviewed in Prior et al, 2012).

**Literature references**


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NF1 is a RAS GAP that stimulates the intrinsic RAS GTPase activity, thereby shifting the RAS pathway towards the inactive state (reviewed in King et al, 2013). Loss-of-function mutations in NF1 have been identified both in germline diseases like neurofibromatosis 1 and in a range of sporadically occurring cancers. These mutations, which range from complete gene deletions to missense or frameshift mutations, generally decrease NF1 protein levels and abrogate RAS GAP activity in the cells, resulting in constitutive RAS pathway activation (reviewed in Maertens and Cichowski, 2014; Tidyman and Rauen, 2009; Ratner and Miller, 2015).

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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).

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In addition to the highly prevalent and activating V600E BRAF mutations, numerous moderately activating and less common mutations have also been identified in human cancers (Forbes et al, 2015). Unlike the case for their highly activating counterparts, signaling through these mutant versions of BRAF depends both upon RAS binding and RAF dimerization (Wan et al, 2004; Freeman et al, 2013; Roring et al, 2012; reviewed in Lito et al, 2013; Lavoie and Therrien, 2015)

### Literature references


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 transactivated 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).

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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


Signaling by RAF1 mutants

Location: Oncogenic MAPK signaling

Stable identifier: R-HSA-9656223

Diseases: Noonan syndrome, cancer, Costello syndrome, LEOPARD syndrome, hypertrophic cardiomyopathy

RAF1, also known as CRAF, is mutated in a number of germline RASopathies including Noonan Syndrome, Costello Syndrome and others, and also at low frequency in a number of cancers (reviewed in Rauen, 2013; Samatar and Poulikakos, 2015). Activating mutations cluster around conserved region 2 (CR2) which is required for regulation of the protein and the activation segment in CR3 (reviewed in Rauen, 2013).

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Activating mutations in MAP2K1 and MAP2K2, the genes encoding MEK1 and MEK2, have been identified at low frequency in a variety of cancers as well as in germline diseases such as Noonan syndrome, cardiofaciocutaneous syndromes and other RASopathies (reviewed in Samatar and Poulilakos, 2014; Bezniakow et al, 2014; Rauen, 2013).

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Signaling by MAPK mutants

Location: Oncogenic MAPK signaling

Stable identifier: R-HSA-9652817

Diseases: cancer

Mutations in ERK proteins (MAPK1 and MAPK2) are rare, with mutations reported in ~8% of cervical cancers and 1.5% of head and neck squamous cell carcinomas (Ojesina et al, 2014; Cancer Genome Atlas, 2015; reviewed in Najafi et al, 2019). MAPK proteins with activating mutations are often still dependent on upstream phosphorylation by MAP2K proteins, but support sustained downstream signaling by virtue of being resistant to inactivating dephosphorylations (reviewed in Samatar and Poulikakos, 2014; Liu et al, 2018).

Literature references


Signaling by MRAS-complex mutants

Location: Oncogenic MAPK signaling

Stable identifier: R-HSA-9660537

Diseases: Noonan syndrome, esophageal carcinoma

A complex of MRAS, SHOC2 and the phosphatase PP1 contributes to the activation of RAF proteins by removing an inhibitory phosphorylation that mediates binding to 14-3-3 (also known as YWHAB) proteins (Rodriguez-Viciano et al, 2006; Young et al, 2013; reviewed in Simanshu et al, 2017; Lavoie and Therrien, 2015). Activating and inactivating mutations in each of the components of this dephosphorylating complex have been identified in RASopathies as well as at low frequency in some cancers (Cordeddu et al, 2009; Hannig et al, 2014; Gripp et al, 2016; Higgin et al, 2017; Motta et al, 2016; Motta et al, 2019a,b).

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