Signaling by KIT in disease

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

13/11/2022
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: 82

This document contains 7 pathways (see Table of Contents)

https://reactome.org
**Signaling by KIT in disease**

**Stable identifier:** R-HSA-9669938

**Diseases:** cancer

KIT signaling is important in several processes including stem cell maintenance, erythropoiesis, mast cell development, lymphopoiesis, melanogenesis and maintenance of interstitial cell of Cajal (Hirota et al, 1998; Chi et al, 2010). Gain-of-function mutations in KIT have been identified at low frequency in a number of diseases, including AML, melanoma and mast and germ cell tumors, and at higher frequency in gastrointestinal stromal tumors (reviewed in Lennartsson and Roonstrand, 2012; Abbaspour Babaei et al, 2016; Roskoski, 2018).

**Literature references**


**Editions**

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Activating mutations in the kinase domain of KIT are found in a small number of cases of AML and melanoma, as well as in myeloproliferative syndromes, mastocytosis and germ cell tumors (Longley et al, 1996; 1999; Nagata et al, 1995; Beghini et al, 2000; Ning et al, 2001; Tian et al, 1999; Kemmer et al, 2004; reviewed in Roskoski, 2018; Meng and Carvajal, 2019). Mutations in the kinase domain and activation loop of KIT (encoded by exons 13, 14 and 17) also arise in gastrointestinal stromal tumors (GIST) as primary mutations (<1%) and as secondary resistance mutations in response to treatment with imatinib (Chen et al, 2004; Serrano et al, 2019; Gajiwala et al, 2008; McLean et al, 2008; reviewed in Antonescu, 2006; Roskoski, 2018; Wu et al, 2019; Corless et al, 2011). Activating kinase mutants of KIT are constitutively active in the absence of ligand and can be tyrosine phosphorylated in the absence of dimerization (Furitsu et al, 1993; Hirota et al, 1998; Tsujimura et al, 1994).

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https://reactome.org
Mutations in the juxtamembrane region of KIT, encoded by exon 11, are especially prevalent as initiating events in gastrointestinal stromal tumors (GIST), but are also found at lower frequency in other cancers such as AML and melanoma (reviewed in Antonescu, 2006; Roskoski, 2018). Mutations in this region of KIT are believed to disrupt an auto-inhibitory function, leading to constitutive enzyme activation (Ma et al, 1999; Chan et al, 2003; Mol et al, 2004; reviewed in Roskoski, 2018). Unlike kinase domain mutants, juxtamembrane domain KIT mutants still undergo dimerization, although in a ligand-independent manner (Hirota et al, 1998; Furitsu et al, 1993; reviewed in Lennartsson and Roonstrand, 2012).

**Literature references**


Many of the described KIT mutations are located in the fifth Ig-like domain, encoded by exon 8 and 9. The fifth Ig-like domain of KIT plays a critical role in stabilizing the receptor dimers formed upon SCF binding, allowing these mutations to support constitutive activation of the receptor (Yuzawa et al, 2007; reviewed in Lennartsson and Ronnstrand, 2012)

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Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Location: Signaling by KIT in disease

Stable identifier: R-HSA-9670439

Diseases: cancer

Activation of the PI3K/mTOR, RAS/MAPK and STAT signaling pathways has been observed downstream of activated extracellular, juxtamembrane and kinase domain mutants of KIT, although downstream signaling has not been studied in great detail in all cases. Activation of these pathways contributes to cellular proliferation, avoidance of apoptosis, and actin cytoskeletal organization (Dunesing et al, 2004; Bauer et al, 2007; Chi et al, 2010; Bosbach et al, 2017; reviewed in Lennartsson and Roonstrand, 2012; Corless et al, 2011).

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KIT mutants bind TKIs

**Location:** Signaling by KIT in disease

**Stable identifier:** R-HSA-9669921

**Diseases:** cancer

Aberrant signaling by activated forms of KIT can be inhibited by tyrosine kinase inhibitors. Primary mutations in KIT are frequently found in exon 11, encoding the juxtamembrane domain responsible for autoinhibition of the kinase. These mutations are generally sensitive to tyrosine kinase inhibitors such as imatinib. Accumulation of secondary mutations in the ATP-binding pocket and the activation loop of the kinase domain contributes to resistance to first line tyrosine kinase inhibitors. KIT receptors with in these regions are sensitive to a panel of additional tyrosine kinase inhibitors such as sunitinib and regorafenib (Serrano et al, 2019; reviewed in Roskoski, 2018; Klug et al, 2018; Serrano et al, 2017).

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Activating mutations in the juxtamembrane domain of KIT are common in some cancers, including gastrointestinal stromal tumors, melanoma and acute myeloid leukemia (reviewed in Roskoski, 2018). These mutations are sensitive to inhibition with imatinib, which in 2001 was the first tyrosine kinase inhibitor approved for treatment of cancer (Demetri et al, 2002; Corless et al, 2011; reviewed in Zitvogel, 2016). Although highly successful in prolonging survival, imatinib-resistance develops in most patients due to appearance of secondary mutations, often in the ATP-binding pocket or in the activation loop of the kinase domain (Gajiwala et al, 2008; Serrano et al, 2019; reviewed in Roskoski, 2018; Napolitano and Vincenzi, 2019).

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