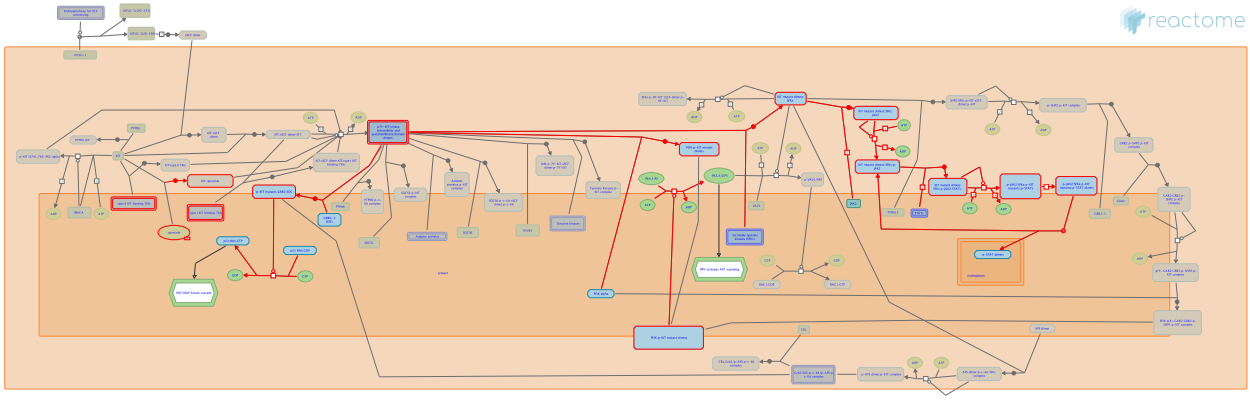
Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants



García-Valverde, A., Pilco-Janeta, D., Rothfels, K., Serrano, C.

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10/09/2021

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

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. ↗

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

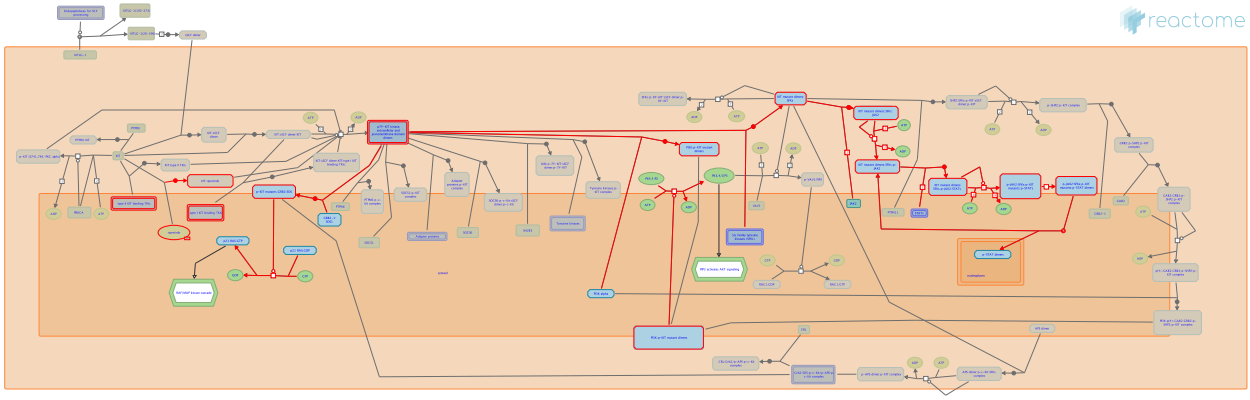
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants ↗

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).

Literature references

Bosbach, B., Rossi, F., Yozgat, Y., Loo, J., Zhang, JQ., Berrozpe, G. et al. (2017). Direct engagement of the PI3K pathway by mutant KIT dominates oncogenic signaling in gastrointestinal stromal tumor. *Proc. Natl. Acad. Sci. U.S.A., 114*, E8448-E8457. ↗

Bauer, S., Duensing, A., Demetri, GD., Fletcher, JA. (2007). KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway. *Oncogene, 26*, 7560-8. ↗

Duensing, A., Medeiros, F., McConarty, B., Joseph, NE., Panigrahy, D., Singer, S. et al. (2004). Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). *Oncogene, 23*, 3999-4006. ↗

Corless, CL., Barnett, CM., Heinrich, MC. (2011). Gastrointestinal stromal tumours: origin and molecular oncology. *Nat. Rev. Cancer, 11*, 865-78. ↗

Chi, P., Chen, Y., Zhang, L., Guo, X., Wongvipat, J., Shamu, T. et al. (2010). ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. *Nature, 467*, 849-53. ↗

Editions

2020-03-13	Reviewed	Serrano, C., Pilco-Janeta, D., García-Valverde, A.
2020-04-01	Authored	Rothfels, K.
2020-05-04	Edited	Rothfels, K.

Phosphorylated KIT mutants bind PI3K ↗

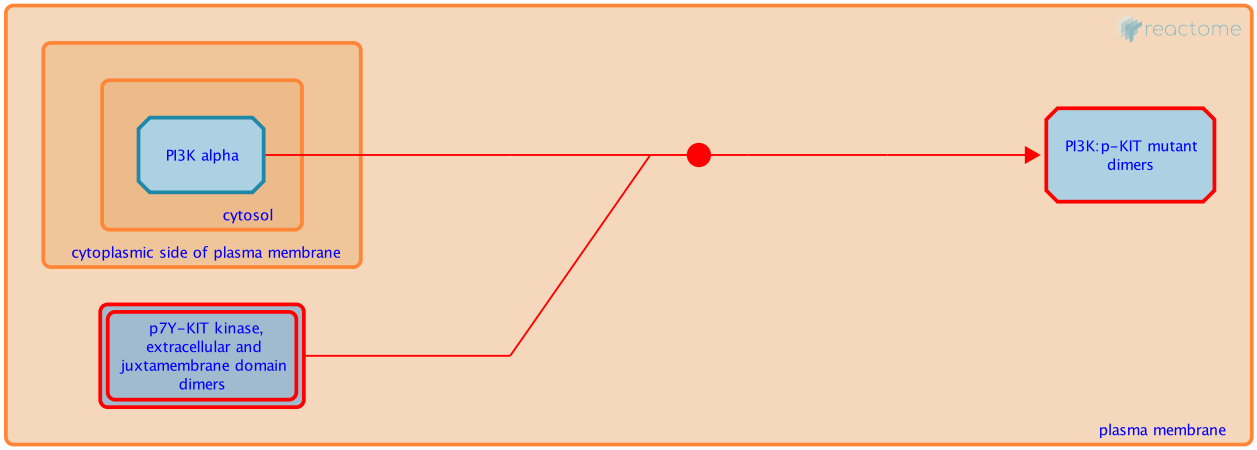
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670431

Type: binding

Compartments: plasma membrane, cytosol, extracellular region

Diseases: cancer



PI3K-mediated signaling has been demonstrated downstream of a number of oncogenic KIT mutants, including extracellular, juxtamembrane and kinase domain mutants (Kemmer et al, 2004; Nakai et al, 2005; Hara et al, 2017; Obata et al, 2017; Duensing et al, 2004; Tarn et al, 2006; Rossi et al, 2006; Bauer et al, 2007; Bosbach et al, 2017; Zhu et al, 2007). In this pathway, KIT mutants are shown directly recruiting PI3K; pathway activation may also involve indirect recruitment through GRB2:GAB2, as in the wild-type pathway (reviewed in Lennnartsson and Roonstrand, 2012; Corless et al, 2011).

Followed by: KIT mutants:PI3K catalyze synthesis of PIP3

Literature references

Kemmer, K., Corless, CL., Fletcher, JA., McGreevey, L., Haley, A., Griffith, D. et al. (2004). KIT mutations are common in testicular seminomas. *Am. J. Pathol., 164*, 305-13. ↗

Nakai, Y., Nonomura, N., Oka, D., Shiba, M., Arai, Y., Nakayama, M. et al. (2005). KIT (c-kit oncogene product) pathway is constitutively activated in human testicular germ cell tumors. *Biochem. Biophys. Res. Commun., 337*, 289-96. ↗

Hara, Y., Obata, Y., Horikawa, K., Tasaki, Y., Suzuki, K., Murata, T. et al. (2017). M-COPA suppresses endolysosomal Kit-Akt oncogenic signalling through inhibiting the secretory pathway in neoplastic mast cells. *PLoS ONE, 12*, e0175514. ↗

Obata, Y., Horikawa, K., Takahashi, T., Akieda, Y., Tsujimoto, M., Fletcher, JA. et al. (2017). Oncogenic signaling by Kit tyrosine kinase occurs selectively on the Golgi apparatus in gastrointestinal stromal tumors. *Oncogene, 36*, 3661-3672. ↗

Tarn, C., Skorobogatko, YV., Taguchi, T., Eisenberg, B., von Mehren, M., Godwin, AK. (2006). Therapeutic effect of imatinib in gastrointestinal stromal tumors: AKT signaling dependent and independent mechanisms. *Cancer Res., 66*, 5477-86. ↗

Editions

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KIT mutants:PI3K catalyze synthesis of PIP3 ↗

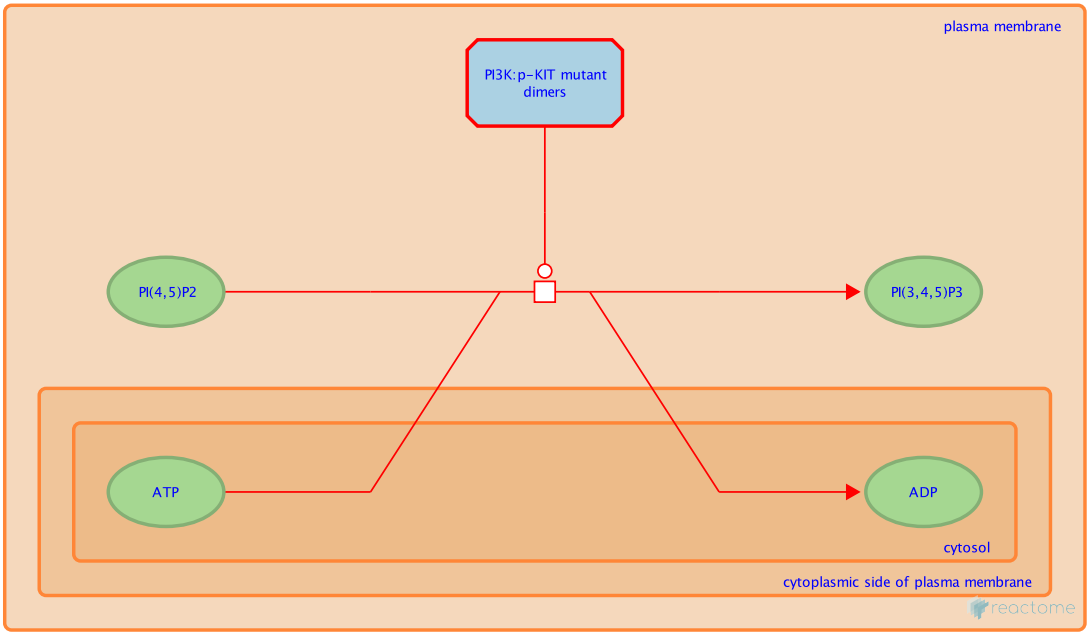
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670433

Type: transition

Compartments: plasma membrane, cytosol, extracellular region

Diseases: cancer



PI3K/AKT signaling is initiated downstream of KIT juxtamembrane and kinase domain mutants, as assessed by the presence of phosphorylated AKT in Western analysis (Kemmer et al, 2004; Nakai et al, 2005; Duensing et al, 2004; Tarn et al, 2006; Rossi et al, 2006; Bauer et al, 2007; Bosbach et al, 2017; Zhu et sl, 2007; Serrano et al, 2019; reviewed in Lennartsson and Roonstrand, 2012).

Preceded by: Phosphorylated KIT mutants bind PI3K

Literature references

Kemmer, K., Corless, CL., Fletcher, JA., McGreevey, L., Haley, A., Griffith, D. et al. (2004). KIT mutations are common in testicular seminomas. *Am. J. Pathol., 164*, 305-13. ↗

Nakai, Y., Nonomura, N., Oka, D., Shiba, M., Arai, Y., Nakayama, M. et al. (2005). KIT (c-kit oncogene product) pathway is constitutively activated in human testicular germ cell tumors. *Biochem. Biophys. Res. Commun., 337*, 289-96. ↗

Bauer, S., Duensing, A., Demetri, GD., Fletcher, JA. (2007). KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway. *Oncogene, 26*, 7560-8. ↗

Duensing, A., Medeiros, F., McConarty, B., Joseph, NE., Panigrahy, D., Singer, S. et al. (2004). Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). *Oncogene, 23*, 3999-4006. ↗

Tarn, C., Skorobogatko, YV., Taguchi, T., Eisenberg, B., von Mehren, M., Godwin, AK. (2006). Therapeutic effect of imatinib in gastrointestinal stromal tumors: AKT signaling dependent and independent mechanisms. *Cancer Res., 66*, 5477-86. ↗

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KIT mutants bind GRB2-SOS ↗

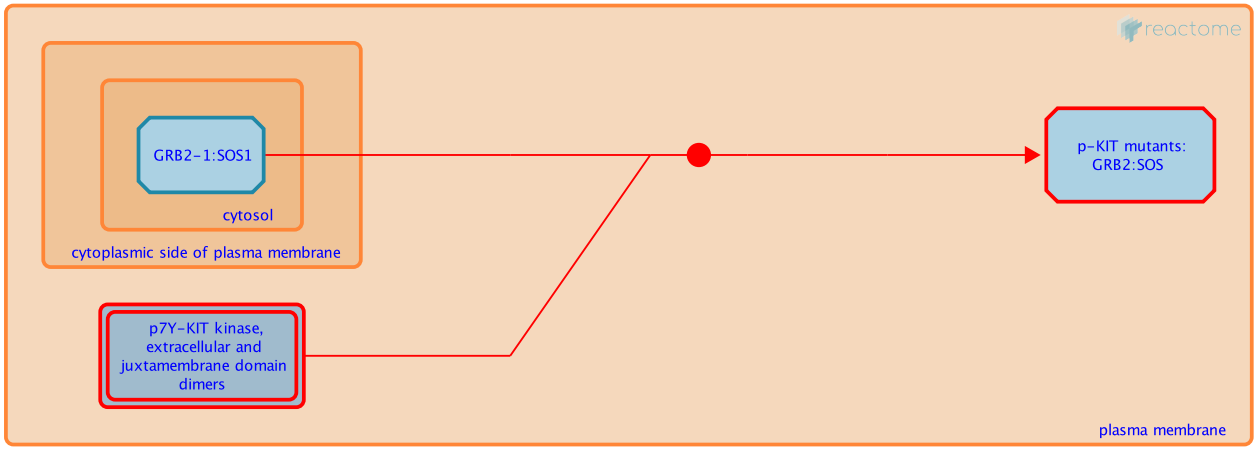
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670428

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



A number of activating extracellular-, juxtamembrane- and kinase-domain KIT mutants are believed to signal through the RAS/MAP kinase cascade, as assessed by the presence of phospho-ERK1 and 2 (also known as MAPK3 and MAPK1). Although the pathway has not been studied in detail, signaling downstream of KIT mutants likely involves recruitment of GRB2:SOS1, as is the case for the wild-type receptor Frost et al, 2002; Garner et al, 2014; Monsel et al, 2010; Obata et al, 2017; Chi et al, 2010; Ran et al, 2015; Serrano et al, 2015; Zhu et al, 2007; reviewed in Abbaspour Babaei et al, 2016; Lennartsson and Roonstrand, 2012).

Followed by: p-KIT mutants:GRB2:SOS catalyzes nucleotide exchange on RAS

Literature references

Frost, MJ., Ferrao, PT., Hughes, TP., Ashman, LK. (2002). Juxtamembrane mutant V560GKit is more sensitive to Imatinib (STI571) compared with wild-type c-kit whereas the kinase domain mutant D816VKit is resistant. *Mol. Cancer Ther., 1*, 1115-24. ↗

Monsel, G., Ortonne, N., Bagot, M., Bensussan, A., Dumaz, N. (2010). c-Kit mutants require hypoxia-inducible factor 1alpha to transform melanocytes. *Oncogene, 29*, 227-36. ↗

Obata, Y., Horikawa, K., Takahashi, T., Akieda, Y., Tsujimoto, M., Fletcher, JA. et al. (2017). Oncogenic signaling by Kit tyrosine kinase occurs selectively on the Golgi apparatus in gastrointestinal stromal tumors. *Oncogene, 36*, 3661-3672. ↗

Chi, P., Chen, Y., Zhang, L., Guo, X., Wongvipat, J., Shamu, T. et al. (2010). ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. *Nature, 467*, 849-53. ↗

Ran, L., Sirota, I., Cao, Z., Murphy, D., Chen, Y., Shukla, S. et al. (2015). Combined inhibition of MAP kinase and KIT signaling synergistically destabilizes ETV1 and suppresses GIST tumor growth. *Cancer Discov, 5*, 304-15. ↗

Editions

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2020-05-04	Edited	Rothfels, K.

p-KIT mutants:GRB2:SOS catalyzes nucleotide exchange on RAS ↗

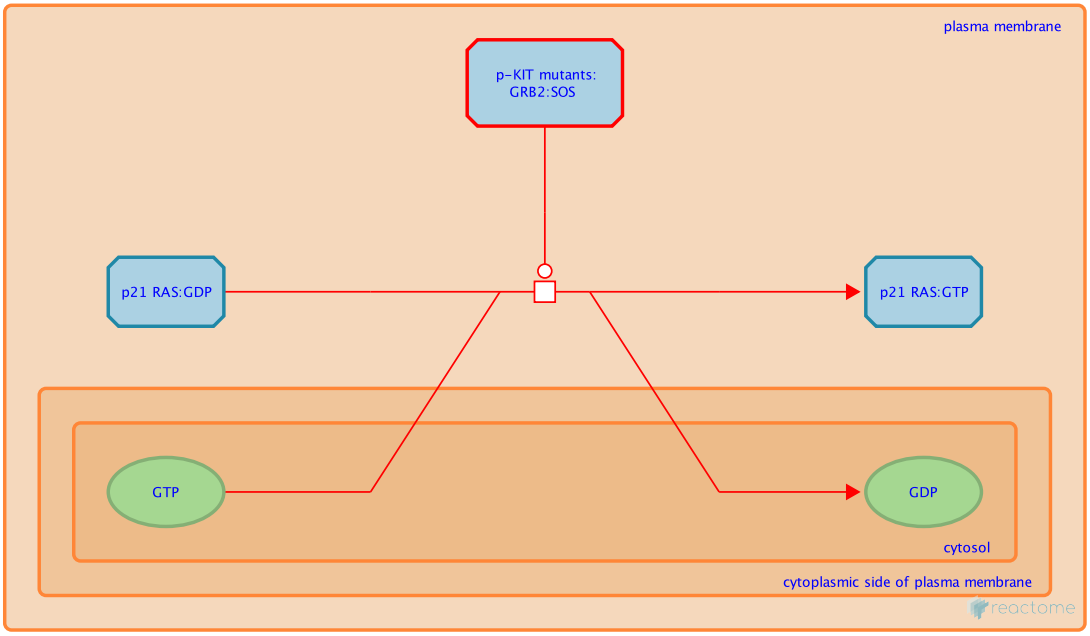
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670436

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer



Activation of the MAP kinase signaling pathway downstream of oncogenic KIT mutants, as evidenced by the presence of phosphorylated ERK proteins, likely depends on the SOS-mediated nucleotide exchange of GDP for GTP on RAS, as is the case for the wild-type receptor (Frost et al, 2002; Chi et al, 2010; Garner et al, 2014; Monsel et al, 2010; Obata et al, 2017; reviewed in Abbaspour Babaei et al, 2016; Lennartsson and Roonstrand, 2012).

Preceded by: KIT mutants bind GRB2-SOS

Literature references

Frost, MJ., Ferrao, PT., Hughes, TP., Ashman, LK. (2002). Juxtamembrane mutant V560GKit is more sensitive to Imatinib (STI571) compared with wild-type c-kit whereas the kinase domain mutant D816VKit is resistant. *Mol. Cancer Ther., 1*, 1115-24. ↗

Garner, AP., Gozgit, JM., Anjum, R., Vodala, S., Schrock, A., Zhou, T. et al. (2014). Ponatinib inhibits polyclonal drug-resistant KIT oncoproteins and shows therapeutic potential in heavily pretreated gastrointestinal stromal tumor (GIST) patients. *Clin. Cancer Res., 20*, 5745-5755. ↗

Monsel, G., Ortonne, N., Bagot, M., Bensussan, A., Dumaz, N. (2010). c-Kit mutants require hypoxia-inducible factor 1alpha to transform melanocytes. *Oncogene, 29*, 227-36. ↗

Obata, Y., Horikawa, K., Takahashi, T., Akieda, Y., Tsujimoto, M., Fletcher, JA. et al. (2017). Oncogenic signaling by Kit tyrosine kinase occurs selectively on the Golgi apparatus in gastrointestinal stromal tumors. *Oncogene, 36*, 3661-3672. ↗

Abbaspour Babaei, M., Kamalidehghan, B., Saleem, M., Huri, HZ., Ahmadipour, F. (2016). Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. *Drug Des Devel Ther, 10*, 2443-59. ↗

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2020-05-04	Edited	Rothfels, K.

KIT mutants bind SFKs ↗

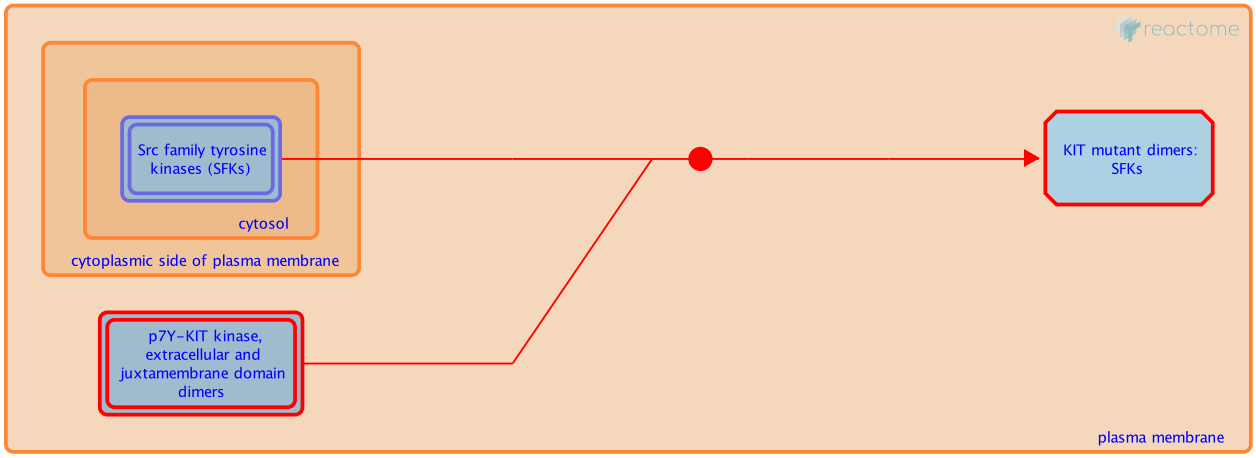
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670414

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



Signaling downstream of KIT mutants occurs in part through SRC family kinases, as is the case for the wild-type receptor (Paronetto et al, 2004; Krystal et al, 1998; Schittenhelm et al, 2006; Tatton et al, 2003; Timokhina et al, 1998; reviewed in Lanneartsson and Roonstrand, 2012). The dependence of different KIT mutants on SRC family signaling varies, however, with mutants such as the common D816V showing less requirement for SFK-mediated signaling (Sun et al, 2009).

Followed by: JAK2 binds to p-KIT mutants

Literature references

Paronetto, MP., Farini, D., Sammarco, I., Maturo, G., Vespasiani, G., Geremia, R. et al. (2004). Expression of a truncated form of the c-Kit tyrosine kinase receptor and activation of Src kinase in human prostatic cancer. *Am. J. Pathol., 164*, 1243-51. ↗

Krystal, GW., DeBerry, CS., Linnekin, D., Litz, J. (1998). Lck associates with and is activated by Kit in a small cell lung cancer cell line: inhibition of SCF-mediated growth by the Src family kinase inhibitor PP1. *Cancer Res, 58*, 4660-6. ↗

Schittenhelm, MM., Shiraga, S., Schroeder, A., Corbin, AS., Griffith, D., Lee, FY. et al. (2006). Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. *Cancer Res., 66*, 473-81. ↗

Tatton, L., Morley, GM., Chopra, R., Khwaja, A. (2003). The Src-selective kinase inhibitor PP1 also inhibits Kit and Bcr-Abl tyrosine kinases. *J. Biol. Chem., 278*, 4847-53. ↗

Timokhina, I., Kissel, H., Stella, G., Besmer, P. (1998). Kit signaling through PI 3-kinase and Src kinase pathways: an essential role for Rac1 and JNK activation in mast cell proliferation. *EMBO J, 17*, 6250-62. ↗

Editions

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2020-05-04	Edited	Rothfels, K.

JAK2 binds to p-KIT mutants ↗

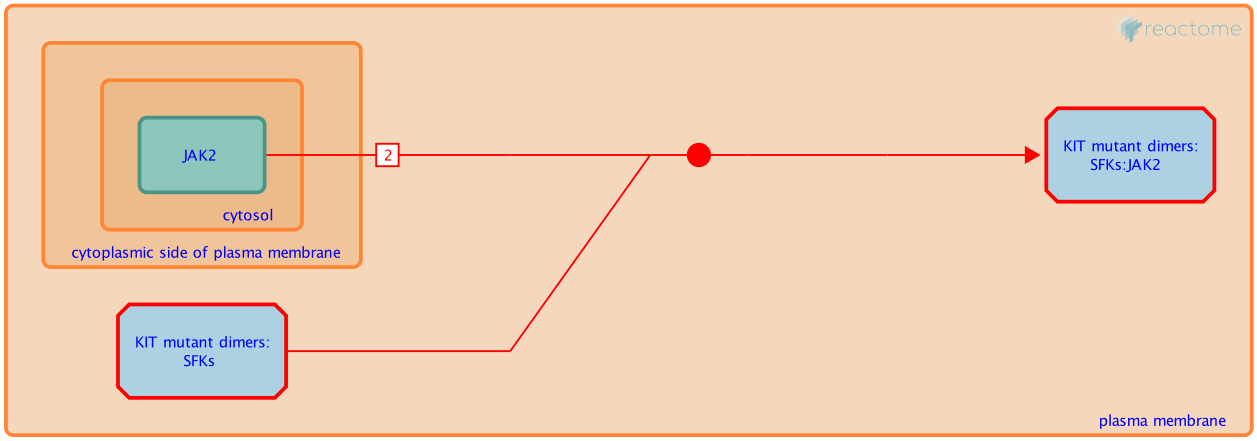
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670413

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



Activation of STAT signaling has been observed downstream of a number of oncogenic KIT mutants, both juxtamembrane and kinase domain mutants, although the biological relevance or each STAT isoform varies between tumor types (Brizzi et al, 1999; Ning et al, 2001; Frost et al, 2002; Growney et al, 2005; Hana et al, 2017; Obata et al, 2017; Duensing et al, 2004; Bauer et al, 2007; Deberry et al, 1997; Ronnstrand, 2004). Although the pathway details haven't been examined in all cases, this likely occurs through the recruitment of JAK2 and SRC family kinases, as is the case for the wild type receptor (reviewed in Lennartsson and Roonstrand, 2012).

Preceded by: KIT mutants bind SFKs

Followed by: Phosphorylation of JAK2 downstream of KIT mutants

Literature references

Brizzi, MF., Dentelli, P., Rosso, A., Yarden, Y., Pegoraro, L. (1999). STAT protein recruitment and activation in c-Kit deletion mutants. *J Biol Chem, 274*, 16965-72. ↗

Ning, ZQ., Li, J., Arceci, RJ. (2001). Signal transducer and activator of transcription 3 activation is required for Asp(816) mutant c-Kit-mediated cytokine-independent survival and proliferation in human leukemia cells. *Blood, 97*, 3559-67. ↗

Growney, JD., Clark, JJ., Adelsperger, J., Stone, R., Fabbro, D., Griffin, JD. et al. (2005). Activation mutations of human c-KIT resistant to imatinib mesylate are sensitive to the tyrosine kinase inhibitor PKC412. *Blood, 106*, 721-4. ↗

Hirota, S., Isozaki, K., Moriyama, Y., Hashimoto, K., Nishida, T., Ishiguro, S. et al. (1998). Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science, 279*, 577-80. ↗

Obata, Y., Horikawa, K., Takahashi, T., Akieda, Y., Tsujimoto, M., Fletcher, JA. et al. (2017). Oncogenic signaling by Kit tyrosine kinase occurs selectively on the Golgi apparatus in gastrointestinal stromal tumors. *Oncogene, 36*, 3661-3672. ↗

Editions

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Phosphorylation of JAK2 downstream of KIT mutants ↗

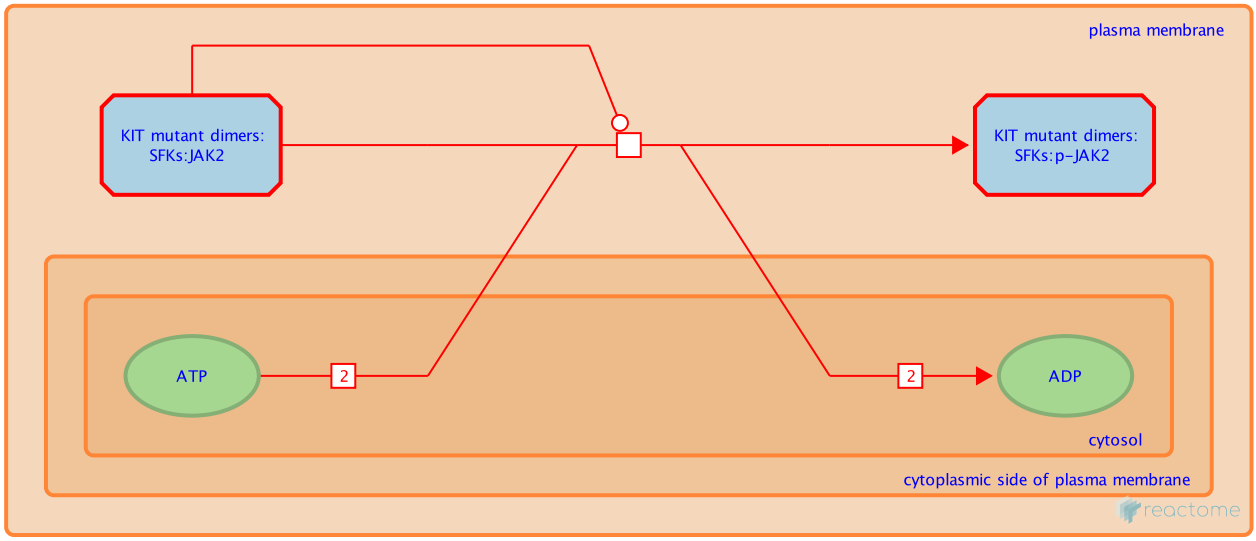
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670418

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer



Although the details haven't been examined in detail in all cases, phosphorylation of JAK2 likely occurs downstream of oncogenic mutations of KIT, as is the case for the wild-type receptor (Brizzi et al, 1999; Ning et al, 2001; Hirota et al, 1998; reviewed in Lennartsson and Roonstrand, 2012).

Preceded by: JAK2 binds to p-KIT mutants

Followed by: Recruitment of STATs by KIT mutants

Literature references

Brizzi, MF., Dentelli, P., Rosso, A., Yarden, Y., Pegoraro, L. (1999). STAT protein recruitment and activation in c-Kit deletion mutants. *J Biol Chem, 274*, 16965-72. ↗

Ning, ZQ., Li, J., Arceci, RJ. (2001). Signal transducer and activator of transcription 3 activation is required for Asp(816) mutant c-Kit-mediated cytokine-independent survival and proliferation in human leukemia cells. *Blood, 97*, 3559-67. ↗

Hirota, S., Isozaki, K., Moriyama, Y., Hashimoto, K., Nishida, T., Ishiguro, S. et al. (1998). Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science, 279*, 577-80. ↗

Lennartsson, J., Rönnstrand, L. (2012). Stem cell factor receptor/c-Kit: from basic science to clinical implications. *Physiol. Rev., 92*, 1619-49. ↗

Editions

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2020-04-01	Authored	Rothfels, K.
2020-05-04	Edited	Rothfels, K.

Recruitment of STATs by KIT mutants ↗

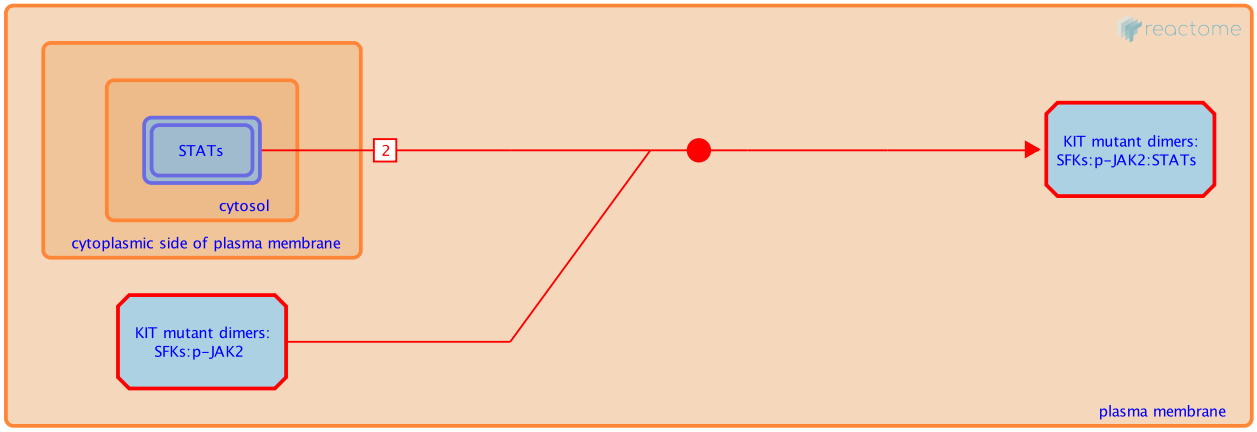
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670416

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



Extracellular- , juxtamembrane- and kinase-domain mutants of KIT have been shown to signal through the STAT pathway, although the biological relevance or each STAT isoform varies between tumor types (Brizzi et al, 1999; Ning et al, 2001; Frost et al, 2002; Growney et al, 2005; Hara et al, 2017; Obata et al, 2017; Duensing et al, 2004; Bauer et al, 2007; Deberry et al, 1997; Ronnstrand, 2004). Although the pathway details haven't been examined in all cases, STAT pathway activation likely occurs through the recruitment of JAK2 and SRC family kinases, as is the case for the wild type receptor (reviewed in Lennartsson and Roonstrand, 2012).

Preceded by: Phosphorylation of JAK2 downstream of KIT mutants

Followed by: Phosphorylation of STATs downstream of KIT mutants

Literature references

Brizzi, MF., Dentelli, P., Rosso, A., Yarden, Y., Pegoraro, L. (1999). STAT protein recruitment and activation in c-Kit deletion mutants. *J Biol Chem, 274*, 16965-72. ↗

Ning, ZQ., Li, J., Arceci, RJ. (2001). Signal transducer and activator of transcription 3 activation is required for Asp(816) mutant c-Kit-mediated cytokine-independent survival and proliferation in human leukemia cells. *Blood, 97*, 3559-67. ↗

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Growney, JD., Clark, JJ., Adelsperger, J., Stone, R., Fabbro, D., Griffin, JD. et al. (2005). Activation mutations of human c-KIT resistant to imatinib mesylate are sensitive to the tyrosine kinase inhibitor PKC412. *Blood, 106*, 721-4. ↗

Hara, Y., Obata, Y., Horikawa, K., Tasaki, Y., Suzuki, K., Murata, T. et al. (2017). M-COPA suppresses endolysosomal Kit-Akt oncogenic signalling through inhibiting the secretory pathway in neoplastic mast cells. *PLoS ONE, 12*, e0175514. ↗

Editions

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2020-05-04	Edited	Rothfels, K.

Phosphorylation of STATs downstream of KIT mutants ↗

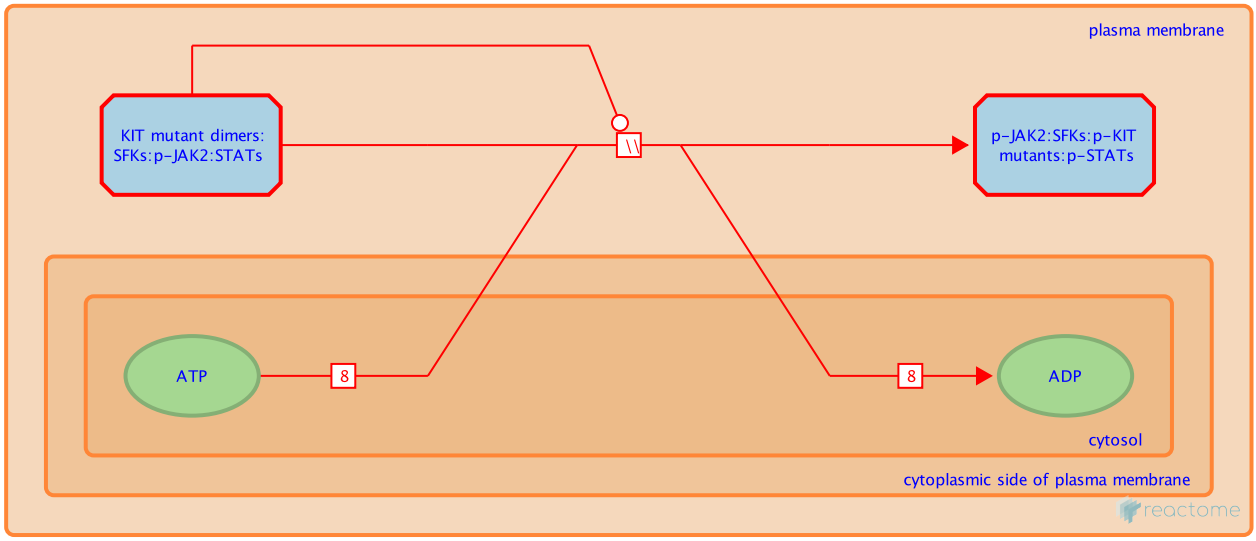
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670412

Type: omitted

Compartments: plasma membrane, cytosol

Diseases: cancer



Extracellular- , juxtamembrane- and kinase-domain mutants of KIT have been shown to activate the STAT pathway, as assessed by STAT phosphorylation. The biological relevance of each STAT isoform varies between tumor types (Brizzi et al, 1999; Ning et al, 2001; Frost et al, 2002; Growney et al, 2005; Hara et al, 2017; Obata et al, 2017; Duensing et al, 2004; Bauer et al, 2007; Deberry et al, 1997; Ronnstrand, 2004; reviewed in Lennartsson and Roonstrand, 2012).

Preceded by: Recruitment of STATs by KIT mutants

Followed by: Dimerization of STATs downstream of KIT mutants

Literature references

Brizzi, MF., Dentelli, P., Rosso, A., Yarden, Y., Pegoraro, L. (1999). STAT protein recruitment and activation in c-Kit deletion mutants. *J Biol Chem, 274*, 16965-72. ↗

Ning, ZQ., Li, J., Arceci, RJ. (2001). Signal transducer and activator of transcription 3 activation is required for Asp(816) mutant c-Kit-mediated cytokine-independent survival and proliferation in human leukemia cells. *Blood, 97*, 3559-67. ↗

Frost, MJ., Ferrao, PT., Hughes, TP., Ashman, LK. (2002). Juxtamembrane mutant V560GKit is more sensitive to Imatinib (STI571) compared with wild-type c-kit whereas the kinase domain mutant D816VKit is resistant. *Mol. Cancer Ther., 1*, 1115-24. ↗

Growney, JD., Clark, JJ., Adelsperger, J., Stone, R., Fabbro, D., Griffin, JD. et al. (2005). Activation mutations of human c-KIT resistant to imatinib mesylate are sensitive to the tyrosine kinase inhibitor PKC412. *Blood, 106*, 721-4. ↗

Hara, Y., Obata, Y., Horikawa, K., Tasaki, Y., Suzuki, K., Murata, T. et al. (2017). M-COPA suppresses endolysosomal Kit-Akt oncogenic signalling through inhibiting the secretory pathway in neoplastic mast cells. *PLoS ONE, 12*, e0175514. ↗

Editions

2020-03-13	Reviewed	Serrano, C., Pilco-Janeta, D., García-Valverde, A.
2020-04-01	Authored	Rothfels, K.
2020-05-04	Edited	Rothfels, K.

Dimerization of STATs downstream of KIT mutants ↗

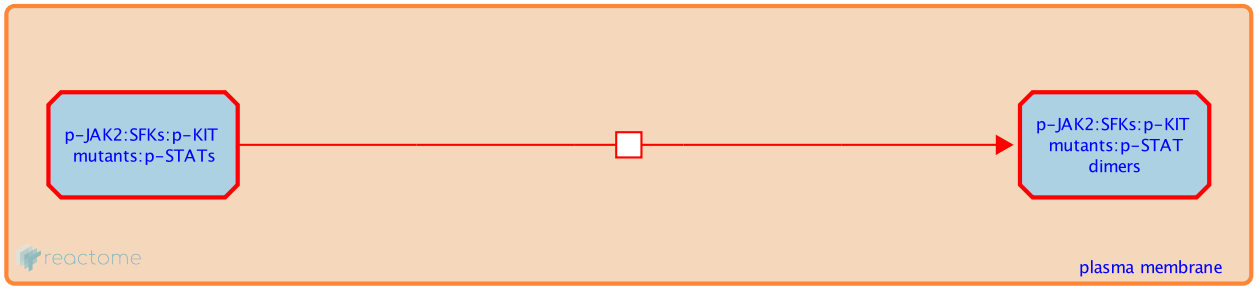
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670417

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer



Activation of STAT signaling suggests that STATs dimerize downstream of activating KIT mutations as is the case with the wild-type receptor, although this hasn't been directly demonstrated in all cases (Brizzi et al, 1999; Ning et al, 2001; Frost et al, 2002; Growney et al, 2005; Hara et al, 2017; Obata et al, 2017; Duensing et al, 2004; Bauer et al, 2007; Deberry et al, 1997; Ronnstrand, 2004; reviewed in Lennartsson and Roonstrand, 2012).

Preceded by: Phosphorylation of STATs downstream of KIT mutants

Followed by: Disassociation and translocation of STATs to the nucleus downstream of KIT mutants

Literature references

Brizzi, MF., Dentelli, P., Rosso, A., Yarden, Y., Pegoraro, L. (1999). STAT protein recruitment and activation in c-Kit deletion mutants. *J Biol Chem, 274*, 16965-72. ↗

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2020-05-04	Edited	Rothfels, K.

Disassociation and translocation of STATs to the nucleus downstream of KIT mutants ↗

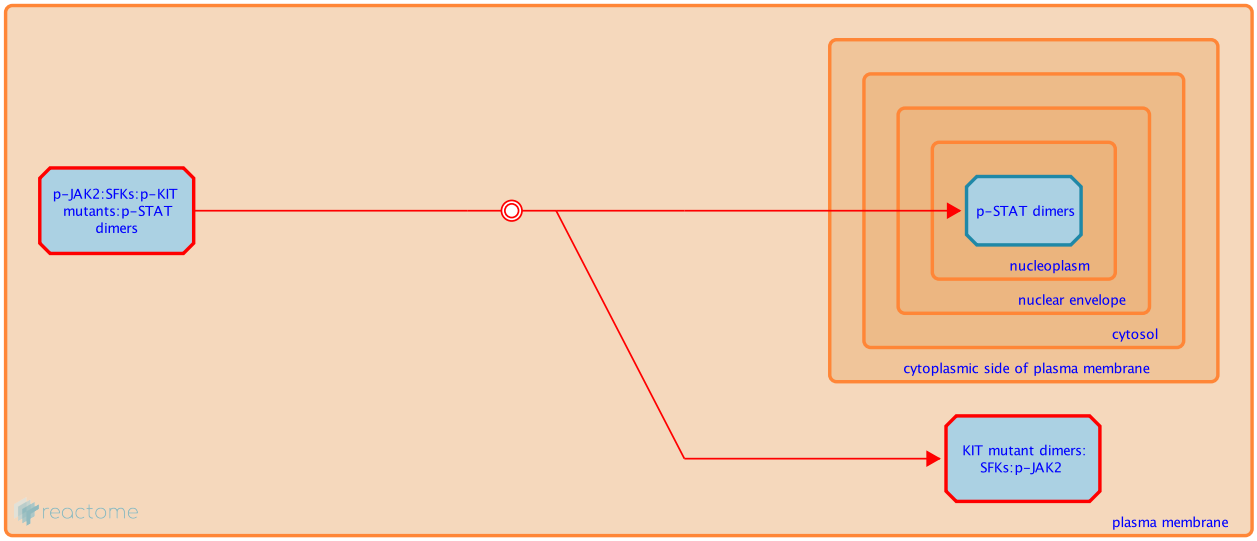
Location: Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants

Stable identifier: R-HSA-9670426

Type: dissociation

Compartments: plasma membrane, cytosol, nucleoplasm

Diseases: cancer



STATs are assumed to dissociate from the receptor and translocate to the nucleus downstream of activated KIT receptors to propagate STAT-dependent signaling (Brizzi et al, 1999; Ning et al, 2001; Frost et al, 2002; Growney et al, 2005; Hara et al, 2017; Obata et al, 2017; Duensing et al, 2004; Bauer et al, 2007; Deberry et al, 1997; Ronnstrand, 2004; reviewed in Lennartsson and Roonstrand, 2012).

Preceded by: Dimerization of STATs downstream of KIT mutants

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