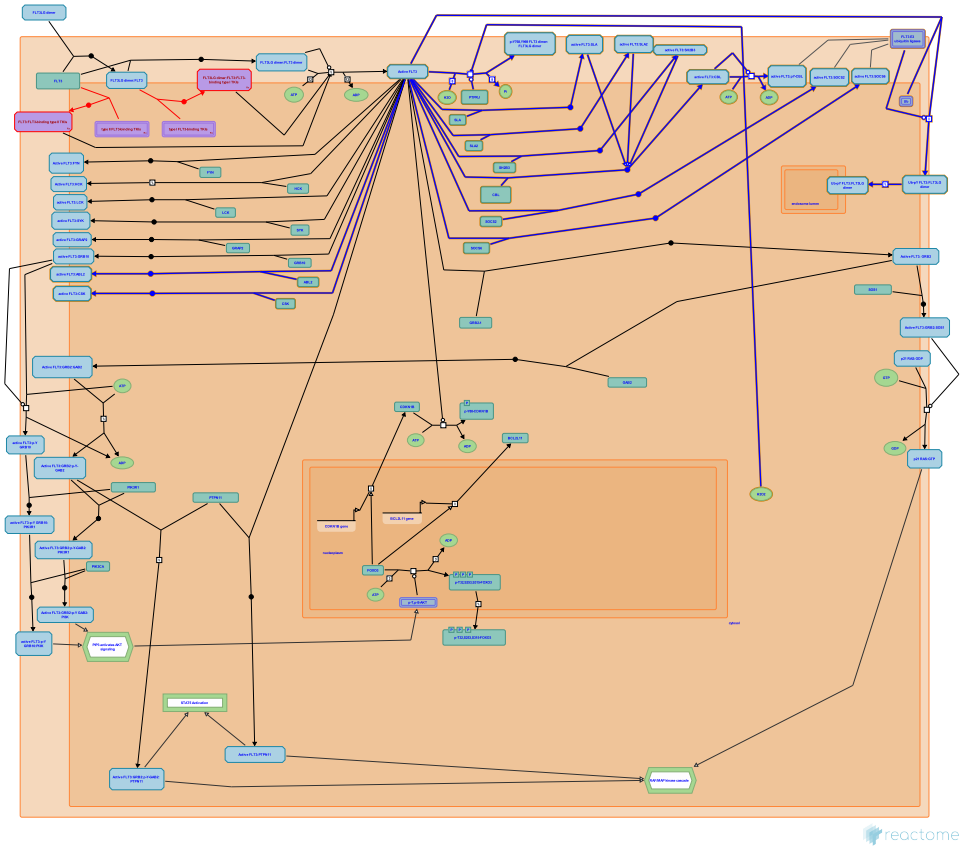
Negative regulation of FLT3



Kazi, JU., Rothfels, K.

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

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.

03/05/2024

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. ↗

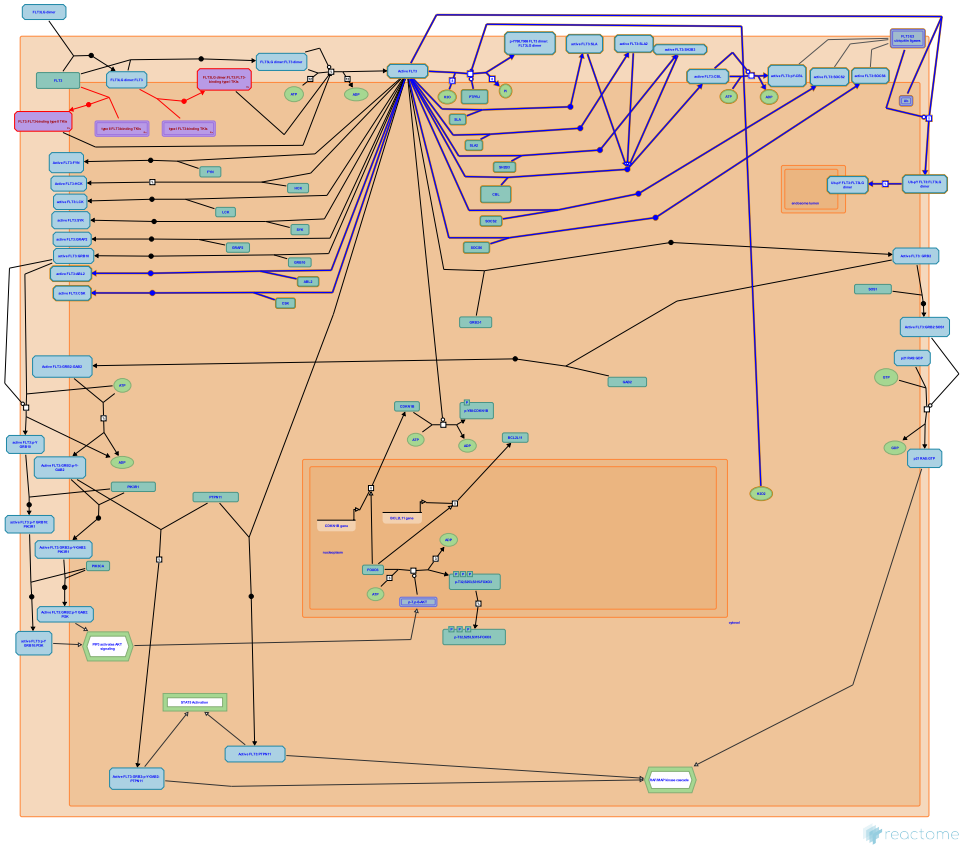
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Negative regulation of FLT3

Stable identifier: R-HSA-9706369



FLT3 activity is negatively regulated through several mechanisms including dephosphorylation, interaction with protein partners that limit downstream signaling pathways, and by ubiquitin-mediated internalization and degradation (reviewed in Kazi and Roonstrand, 2019).

Literature references

Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466.

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

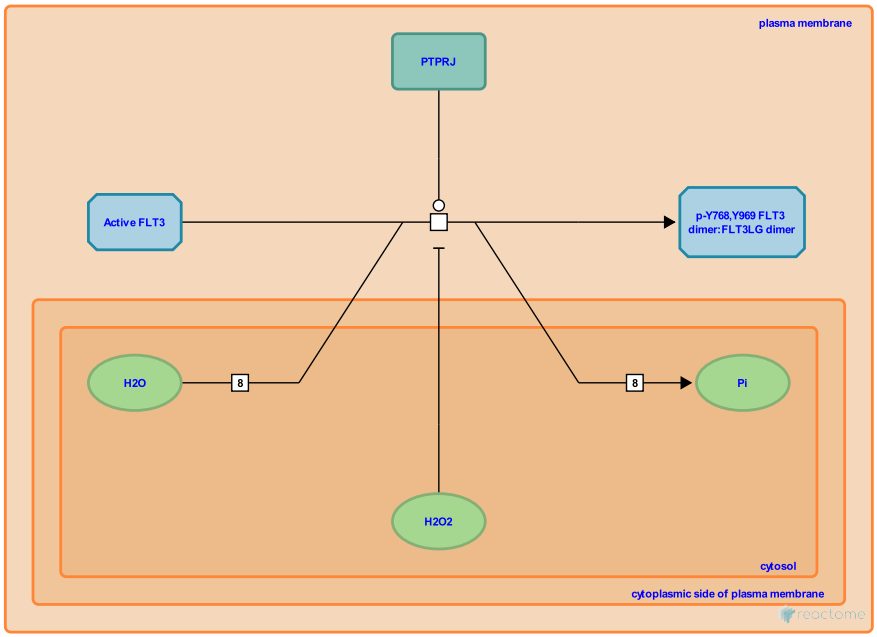
PTPRJ dephosphorylates active FLT3 ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9698408

Type: transition

Compartments: plasma membrane



The protein tyrosine phosphatase PTPRJ (also known as DEP1) dephosphorylates active FLT3 on juxtamembrane tyrosine residues Y589, Y591 and Y599 and Y955 and on kinase domain tyrosine residues Y842 (not shown) and Y955. Dephosphorylation negative regulates FLT3-dependent signaling, particularly through the ERK and PLCgamma pathways, with moderate effects on STAT signaling and minor effects on signaling through AKT (Arora et al, 2011). Dephosphorylation is effected through a direct interaction between the phosphatase and the active receptor. Depletion of PTPRJ by shRNA caused proliferation and colony formation of the mouse myeloid cell line 32D in the presence of ligand but did not promote myeloid disease development (Arora et al, 2011). FLT3 ITD mutants also directly interact with PTPRJ, but autophosphorylation of the mutant receptors is not affected by PTPRJ depletion (Arora et al, 2011). FLT3 ITD insensitivity to PTPTJ-mediated dephosphorylation is the result of increased reactive oxygen (ROS) levels in FLT3 mutants cells, which inactivate the catalytic activity of PTPRJ (Sallmyr et al, 2008; Reddy et al, 2011; Godfrey et al, 2012; Kresinsky et al, 2015; Jayavelu et al, 2016; reviewed in Jayavelu et al, 2016).

Literature references

Cotter, TG., Jayavelu, AK., Böhmer, FD., Moloney, JN. (2016). NOX-driven ROS formation in cell transformation of FLT3-ITD-positive AML. *Exp. Hematol., 44*, 1113-1122. ↗

Bauer, R., Godfrey, R., Müller, JP., Schnetzke, U., Dagnell, M., Böhmer, SA. et al. (2012). Cell transformation by FLT3 ITD in acute myeloid leukemia involves oxidative inactivation of the tumor suppressor protein-tyrosine phosphatase DEP-1/ PTPRJ. *Blood, 119*, 4499-511. ↗

Salgia, R., Griffin, JD., Reddy, MM., Sattler, M., Levine, RL., Fernandes, MS. (2011). NADPH oxidases regulate cell growth and migration in myeloid cells transformed by oncogenic tyrosine kinases. *Leukemia, 25*, 281-9. ↗

Valent, P., Frey, S., Böhmer, SA., Fischer, T., Schröder, K., Serve, H. et al. (2016). NOX4-driven ROS formation mediates PTP inactivation and cell transformation in FLT3ITD-positive AML cells. *Leukemia, 30*, 473-83. ↗

Sallmyr, A., Grosu, D., Rassool, F., Small, D., Shapiro, P., Datta, K. et al. (2008). Internal tandem duplication of FLT3 (FLT3/ITD) induces increased ROS production, DNA damage, and misrepair: implications for poor prognosis in AML. *Blood, 111*, 3173-82. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

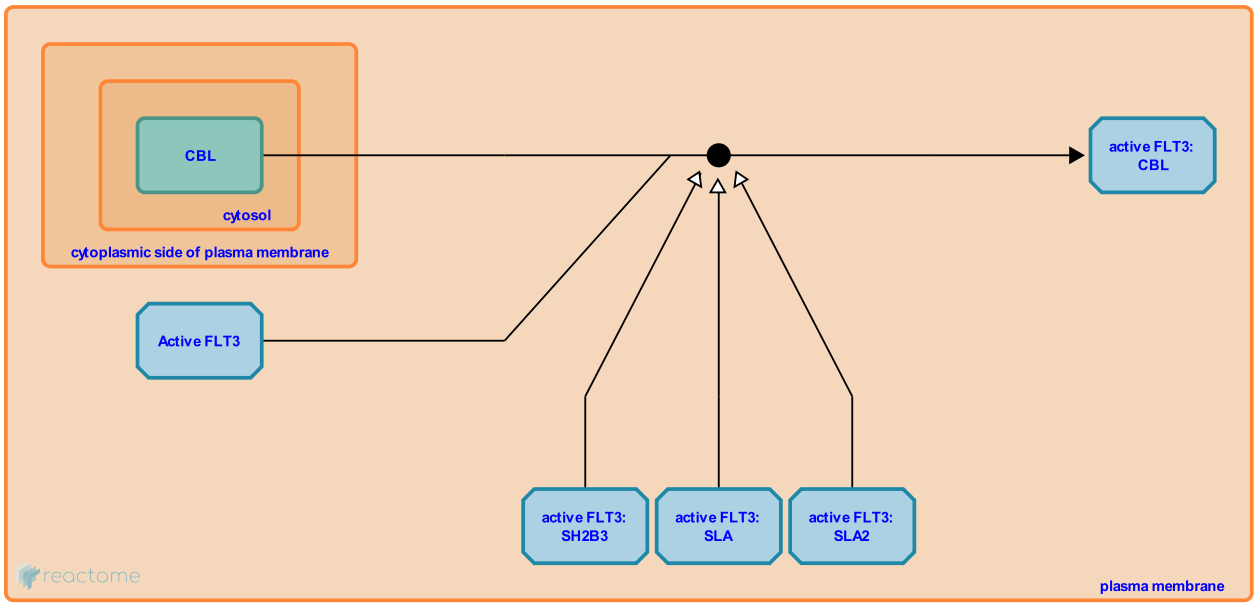
Active FLT3 binds to CBL ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706293

Type: binding

Compartments: plasma membrane, cytosol



Active FLT3 is bound by the E3 ubiquitin protein ligase CBL. In addition to direct interaction with the FLT3 receptor, CBL may also interact indirectly through GRB2. CBL interacts with the receptor in a FL ligand-dependent way, and mutation of FLT3 tyrosine residues Y589 and Y599 abrogates FLT3-dependent CBL phosphorylation (Sargin et al, 2007; Reindl et al, 2009; Heiss et al, 2006). FLT3-mediated phosphorylation of CBL promotes receptor ubiquitination and internalization, consistent with what is observed with other Type III receptor tyrosine kinases (reviewed in Kazi and Ronnstrand, 2019).

Followed by: FLT3 phosphorylates CBL

Literature references

Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466. ↗

Masson, K., Sun, J., Bengtsson, S., Pedersen, M., Heiss, E., Sundberg, C. et al. (2006). Identification of Y589 and Y599 in the juxtamembrane domain of Flt3 as ligand-induced autophosphorylation sites involved in binding of Src family kinases and the protein tyrosine phosphatase SHP2. *Blood, 108*, 1542-50. ↗

Buske, C., Duyster, J., Reindl, C., Spiekermann, K., Vempati, S., Bohlander, SK. et al. (2009). CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes. *Clin Cancer Res, 15*, 2238-47. ↗

Berdel, WE., Grundler, R., Serve, H., Duyster, J., Brandts, C., Tickenbrock, L. et al. (2007). Flt3-dependent transformation by inactivating c-Cbl mutations in AML. *Blood, 110*, 1004-12. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

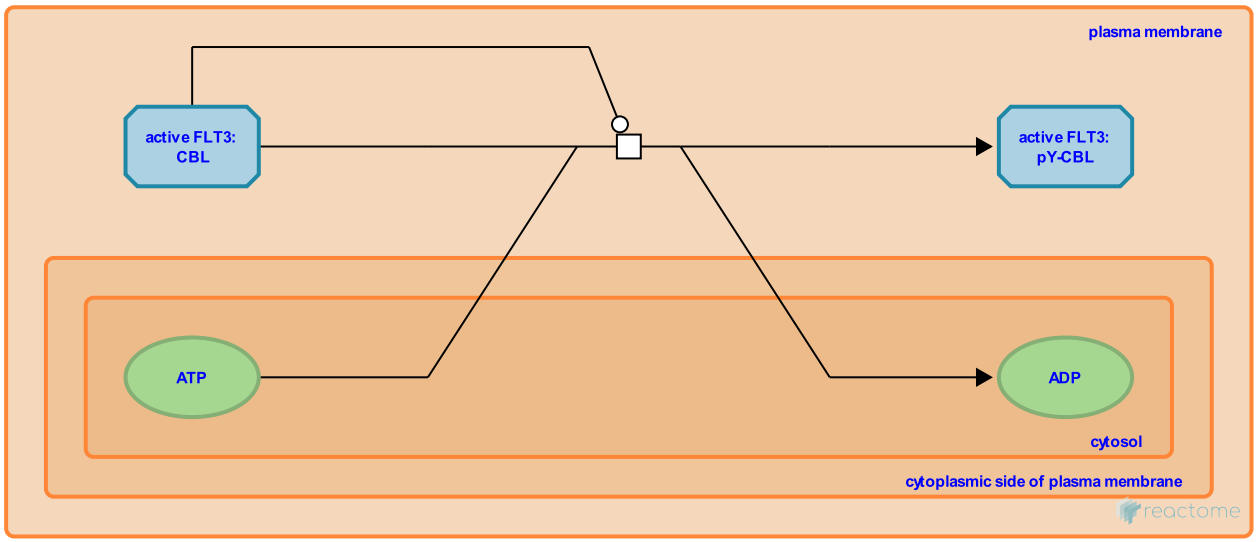
FLT3 phosphorylates CBL ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706350

Type: transition

Compartments: plasma membrane



FLT3 activation leads to tyrosine phosphorylation of CBL (Sargin et al, 2007; Reindl et al, 2009). Phosphorylation of CBL is abolished in FLT3 Y589 and Y599 mutants (Heiss et al, 2006).

Preceded by: Active FLT3 binds to CBL

Followed by: Ubiquitination of FLT3

Literature references

Masson, K., Sun, J., Bengtsson, S., Pedersen, M., Heiss, E., Sundberg, C. et al. (2006). Identification of Y589 and Y599 in the juxtamembrane domain of Flt3 as ligand-induced autophosphorylation sites involved in binding of Src family kinases and the protein tyrosine phosphatase SHP2. *Blood, 108*, 1542-50. ↗

Buske, C., Duyster, J., Reindl, C., Spiekermann, K., Vempati, S., Bohlander, SK. et al. (2009). CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes. *Clin Cancer Res, 15*, 2238-47. ↗

Berdel, WE., Grundler, R., Serve, H., Duyster, J., Brandts, C., Tickenbrock, L. et al. (2007). Flt3-dependent transformation by inactivating c-Cbl mutations in AML. *Blood, 110*, 1004-12. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

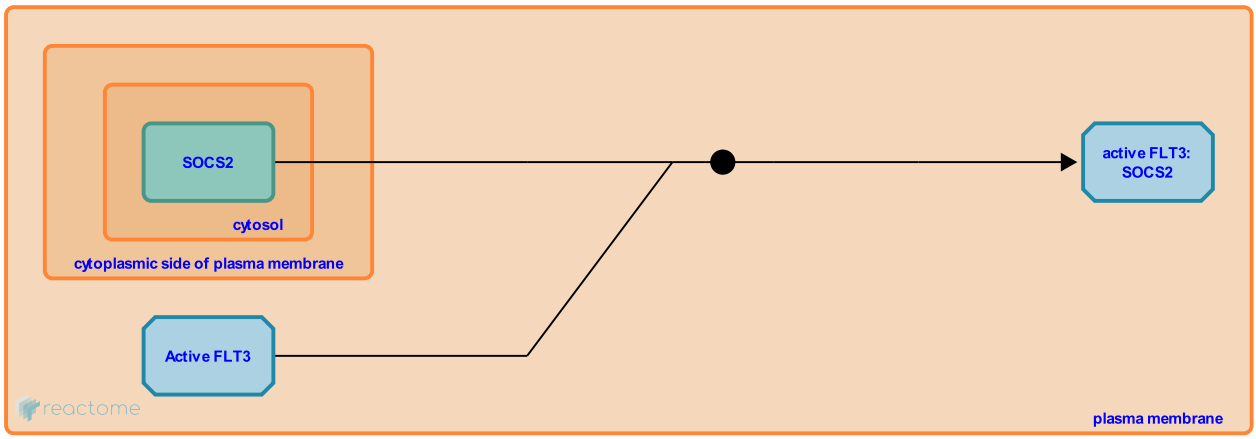
Active FLT3 binds to SOCS2 ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706328

Type: binding

Compartments: plasma membrane, cytosol



The E3 ubiquitin ligase SOCS2 binds to tyrosine phosphorylated FLT3 through Y589 and Y919. SOCS2 contributes to ubiquitination, internalization and downregulation of active FLT3, consistent with known roles for SOCS family members (Kazi and Ronnstrand, 2013; reviewed in Kazi et al, 2014).

Literature references

Flores-Morales, A., Kazi, JU., Kabir, NN., Rönnstrand, L. (2014). SOCS proteins in regulation of receptor tyrosine kinase signaling. *Cell Mol Life Sci, 71*, 3297-310. ↗

Kazi, JU., Rönnstrand, L. (2013). Suppressor of cytokine signaling 2 (SOCS2) associates with FLT3 and negatively regulates downstream signaling. *Mol Oncol, 7*, 693-703. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

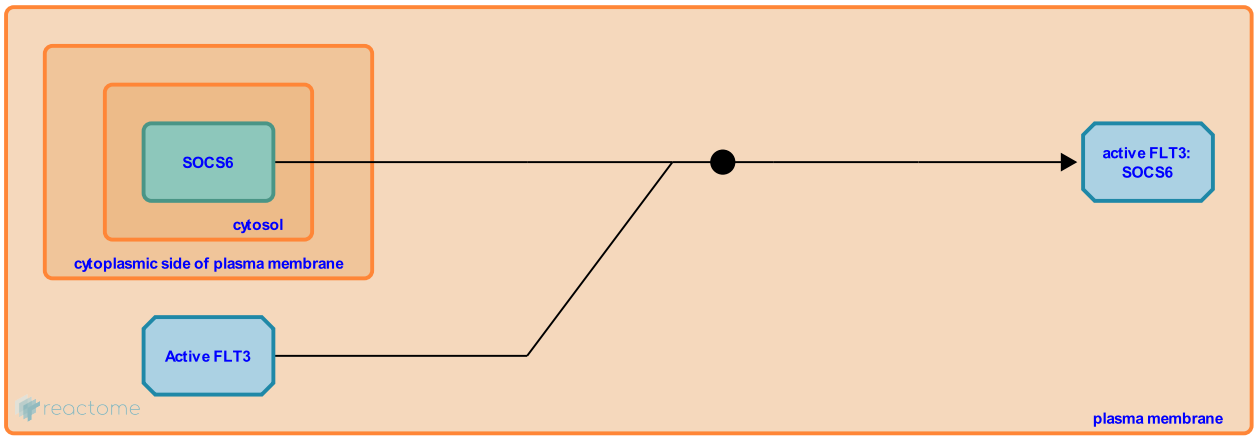
Active FLT3 binds to SOCS6 ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706330

Type: binding

Compartments: plasma membrane, cytosol



The E3 ubiquitin ligase SOCS6 binds to tyrosine phosphorylated FLT3 through Y591 and Y919. SOCS6 contributes to the ubiquitination and degradation of the active FLT3 receptor (Kazi et al, 2012; reviewed in Kazi et al, 2014).

Literature references

Flores-Morales, A., Kazi, JU., Kabir, NN., Rönnstrand, L. (2014). SOCS proteins in regulation of receptor tyrosine kinase signaling. *Cell Mol Life Sci, 71*, 3297-310. ↗

Flores-Morales, A., Kazi, JU., Sun, J., Zadjali, F., Phung, B., Rönnstrand, L. (2012). Suppressor of cytokine signaling 6 (SOCS6) negatively regulates Flt3 signal transduction through direct binding to phosphorylated tyrosines 591 and 919 of Flt3. *J Biol Chem, 287*, 36509-17. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

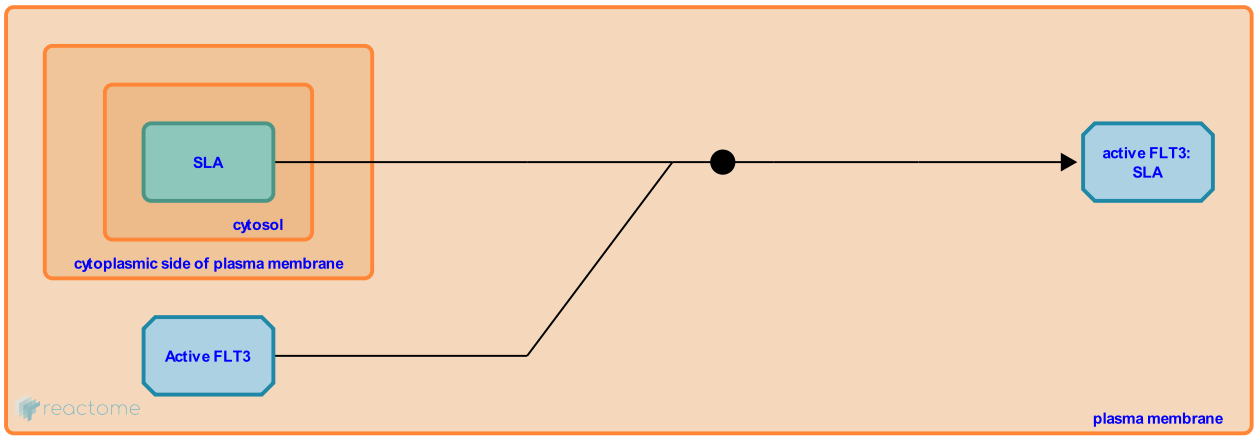
Active FLT3 binds to SLA ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706319

Type: binding

Compartments: plasma membrane, cytosol



SRC-like adaptor protein (SLA, also known as SLAP) binds to tyrosine phosphorylated FLT3 (Kazi and Ronnstrand, 2012). This binding stimulates CBL-dependent FLT3 ubiquitination and internalization. Because SLAP is also known to bind to CBL, SLAP may function as an adaptor protein, bringing CBL to the FLT3 receptor. Direct interaction of CBL and SLAP has not be explicitly demonstrated in the context of FLT3 signaling, however (Dragone et al, 2006; Kazi et al, 2012, reviewed in Kazi and Ronnstrand, 2019). In addition to promoting the internalization of FLT3, SLAP also contributes to downstream signaling through the AKT, MAP kinase and p38 cascades. These roles are not shown in this pathway, however (Kazi et al, 2012).

Literature references

Dragone, LL., White, C., Gadwal, S., Weiss, A., Gu, H., Myers, MD. et al. (2006). Src-like adaptor protein (SLAP) regulates B cell receptor levels in a c-Cbl-dependent manner. *Proc Natl Acad Sci U S A, 103*, 18202-7. ↗

Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466. ↗

Kazi, JU., Rönnstrand, L. (2012). Src-Like adaptor protein (SLAP) binds to the receptor tyrosine kinase Flt3 and modulates receptor stability and downstream signaling. *PLoS One, 7*, e53509. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

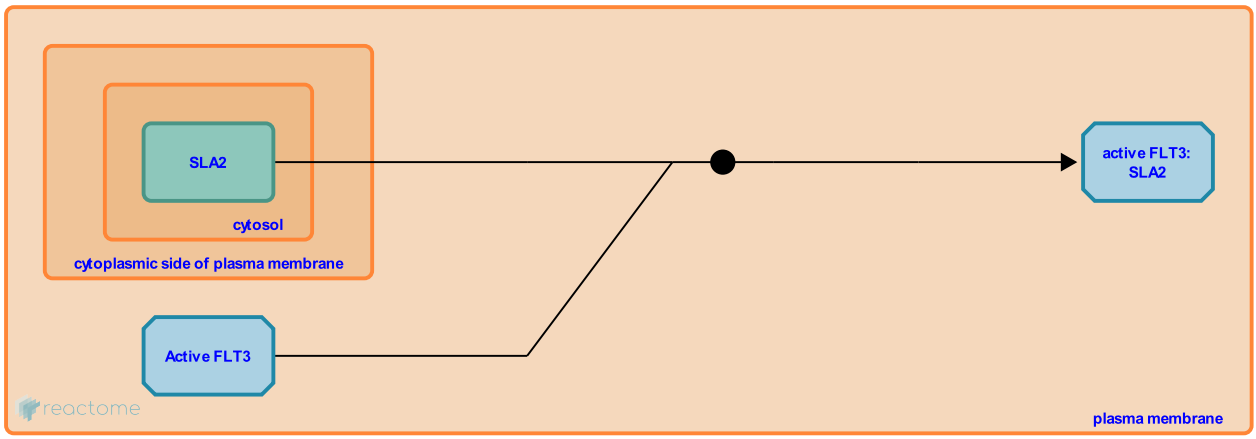
Active FLT3 binds to SLA2

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706323

Type: binding

Compartments: plasma membrane, cytosol



SRC-like adaptor protein 2 (SLA2, also known as SLAP2) binds to tyrosine-phosphorylated FLT3 mainly through Y589 and Y591. Binding of SLA2 inhibits downstream signaling through AKT, MAP kinase and the p38 cascades and promotes receptor ubiquitination and internalization (Moharram et al, 2012). Because SLA2 is a known interactor of CBL, it is possible SLA2 indirectly recruits CBL to FLT3 to promote its downregulation, although this has not been explicitly demonstrated (Loreto et al, 2002; Moharram et al, 2012; reviewed in Kazi and Ronnstrand, 2019).

Literature references

Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466.

Kazi, JU., Li, T., Zhao, H., Sun, J., Su, X., Chougule, RA. et al. (2016). Src-like adaptor protein 2 (SLAP2) binds to and inhibits FLT3 signaling. *Oncotarget, 7*, 57770-57782.

Loreto, MP., Berry, DM., McGlade, CJ. (2002). Functional cooperation between c-Cbl and Src-like adaptor protein 2 in the negative regulation of T-cell receptor signaling. *Mol Cell Biol, 22*, 4241-55.

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

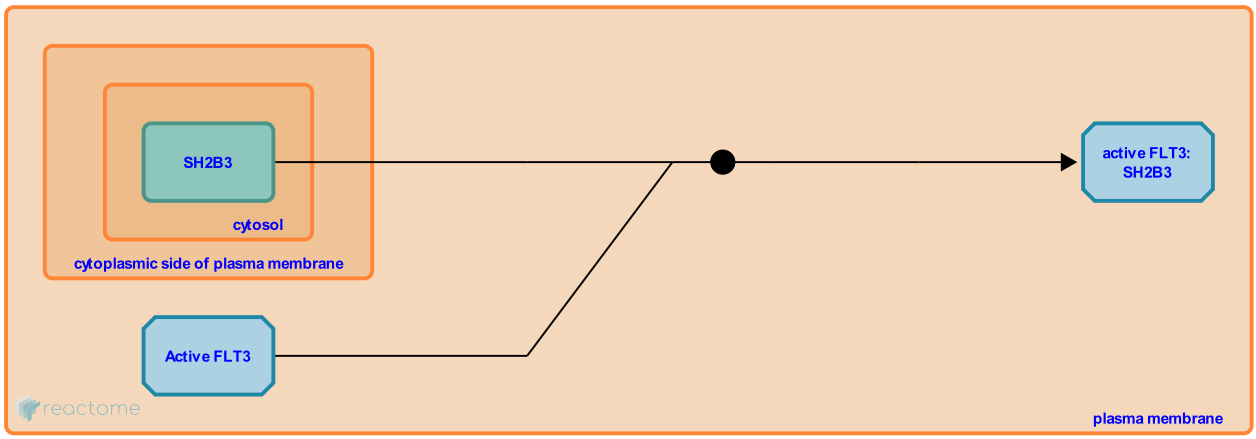
Active FLT3 binds to SH2B3 ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706315

Type: binding

Compartments: plasma membrane, cytosol



SH2B3 (also called LNK) is an adaptor protein that binds to tyrosine phosphorylated FLT3 through at least 3 tyrosine residues, Y572, Y591 and Y919 (Lin et al, 2012). SH3B2 is a known CBL interactor, so may contribute to FLT3 downregulation by promoting the CBL-dependent ubiquitination and internalization of the receptor, although this hasn't been formally demonstrated (Lv et al, 2017; Lin et al, 2012; reviewed in Kazi and Ronnstrand, 2019).

Literature references

Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466. ↗

Tabayashi, T., Koren-Michowitz, M., Lin, DC., Kazi, JU., Gery, S., Yin, T. et al. (2012). Adaptor protein Lnk binds to and inhibits normal and leukemic FLT3. *Blood, 120*, 3310-7. ↗

Hexner, EO., Cheng, Y., Pillai, V., Rozenova, K., Todd, EA., Riling, CR. et al. (2017). CBL family E3 ubiquitin ligases control JAK2 ubiquitination and stability in hematopoietic stem cells and myeloid malignancies. *Genes Dev, 31*, 1007-1023. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

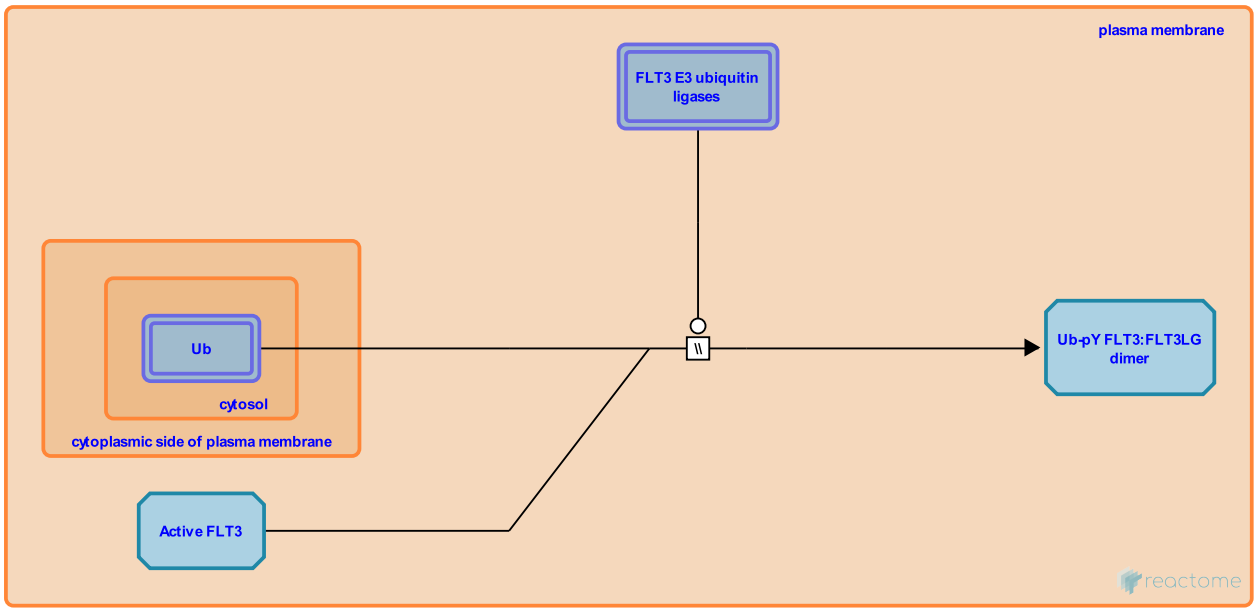
Ubiquitination of FLT3 ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706354

Type: omitted

Compartments: plasma membrane



FLT3 activity is negatively regulated by ubiquitin-mediated internalization (Sargin et al, 2007; Reindl et al, 2009; reviewed in Kazi and Ronnstrand, 2019). Several E3 ubiquitin ligases are implicated in the downregulation of active FLT3 including CBL, SOCS2 and SOCS6 (Sargin et al, 2007, Reindl et al, 2009; Kazi and Ronnstrand, 2013; Kazi et al, 2012).
Ubiquitination of human FLT3 in COS-7 cells is abrogated by the expression of a dominant negative form of CBL, implicating CBL as a major E3 ubiquitin ligase for the FLT3 receptor (Sargin et al, 2007). While direct ubiquitination of FLT3 by SOCS2 and SOCS6 has not been demonstrated, overexpression of these E3 ligases induces FLT3 ubiquitination and internalization in cell lines (Kazi and Ronnstrand, 2012; Kazi and Ronnstrand, 2013; reviewed in Kazi and Ronnstrand, 2019).

Preceded by: FLT3 phosphorylates CBL

Followed by: Internalization of ubiquitinated FLT3

Literature references

Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466. ↗

Buske, C., Duyster, J., Reindl, C., Spiekermann, K., Vempati, S., Bohlander, SK. et al. (2009). CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes. *Clin Cancer Res, 15*, 2238-47. ↗

Kazi, JU., Rönnstrand, L. (2013). Suppressor of cytokine signaling 2 (SOCS2) associates with FLT3 and negatively regulates downstream signaling. *Mol Oncol, 7*, 693-703. ↗

Flores-Morales, A., Kazi, JU., Sun, J., Zadjali, F., Phung, B., Rönnstrand, L. (2012). Suppressor of cytokine signaling 6 (SOCS6) negatively regulates Flt3 signal transduction through direct binding to phosphorylated tyrosines 591 and 919 of Flt3. *J Biol Chem, 287*, 36509-17. ↗

Berdel, WE., Grundler, R., Serve, H., Duyster, J., Brandts, C., Tickenbrock, L. et al. (2007). Flt3-dependent transformation by inactivating c-Cbl mutations in AML. *Blood, 110*, 1004-12. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

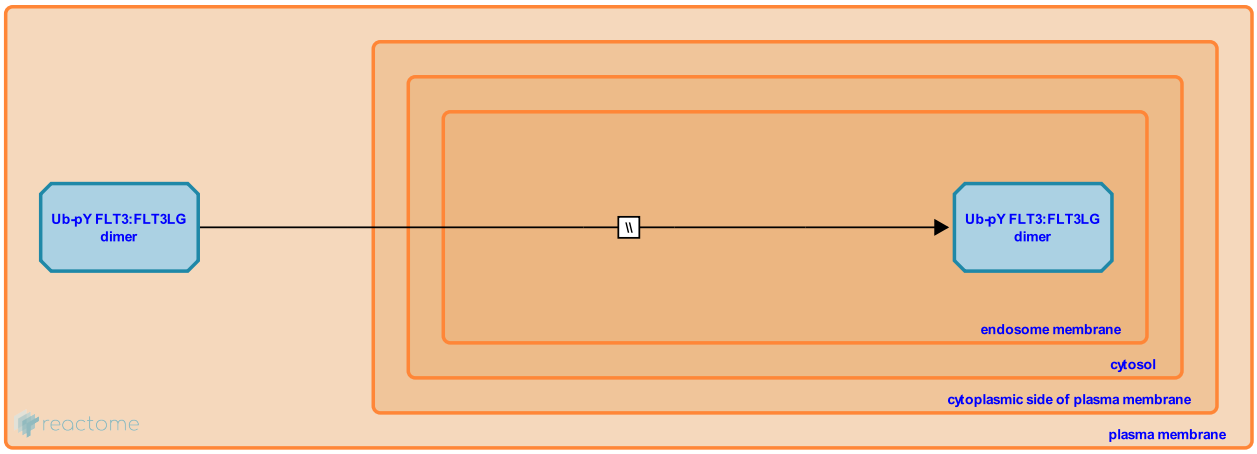
Internalization of ubiquitinated FLT3 ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706364

Type: omitted

Compartments: endosome membrane, plasma membrane



E3 ligase- mediated ubiquitination of FLT3 leads to its internalization to the endosomal compartment (Sargin et al, 2007; Reindl et al, 2009; reviewed in Kazi and Ronnstrand, 2019).

Preceded by: Ubiquitination of FLT3

Literature references

Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466. ↗

Buske, C., Duyster, J., Reindl, C., Spiekermann, K., Vempati, S., Bohlander, SK. et al. (2009). CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes. *Clin Cancer Res, 15*, 2238-47. ↗

Berdel, WE., Grundler, R., Serve, H., Duyster, J., Brandts, C., Tickenbrock, L. et al. (2007). Flt3-dependent transformation by inactivating c-Cbl mutations in AML. *Blood, 110*, 1004-12. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

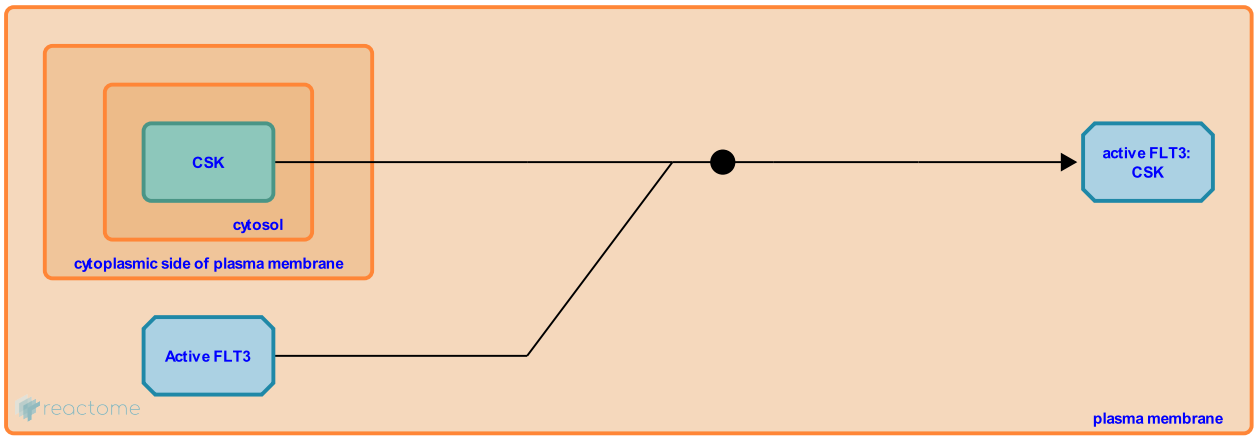
Active FLT3 binds to CSK ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706298

Type: binding

Compartments: plasma membrane, cytosol



The COOH-terminal SRC kinase (CSK) interacts with FLT3 in a phosphorylation-dependent manner through the SH2 domain of CSK. Interaction with CSK downregulates FLT3-dependent signaling through the AKT and MAP kinase pathway without affecting receptor ubiquitination or stability. Consistent with this, siRNA depletion of CSK increased GAB2 and PTPN11 phosphorylation (Kazi et al, 2013; reviewed in Kazi and Ronnstrand, 2019).

Literature references

Vaapil, M., Bracco, E., Agarwal, S., Kazi, JU., Påhlman, S., Rönnstrand, L. (2013). The tyrosine kinase CSK associates with FLT3 and c-Kit receptors and regulates downstream signaling. *Cell Signal, 25*, 1852-60. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

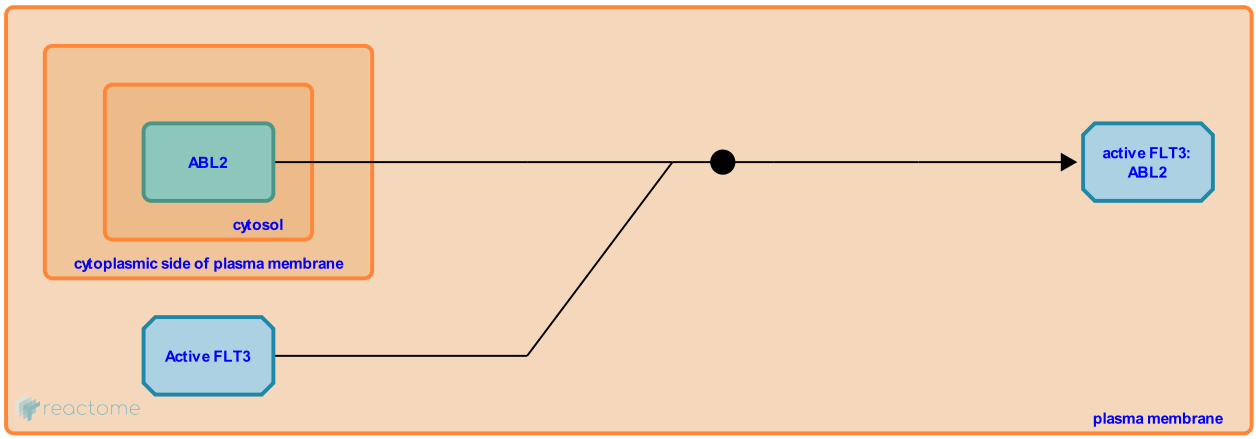
Active FLT3 binds to ABL2 ↗

Location: Negative regulation of FLT3

Stable identifier: R-HSA-9706287

Type: binding

Compartments: plasma membrane, cytosol



The Abelson (ABL) family of non-receptor tyrosine kinase 2 (ABL2, also known as ARG) binds to tyrosine phosphorylated FLT3. ABL2 binding inhibits FLT3-dependent AKT signaling without affecting other downstream pathways like the MAP kinase and STAT cascades, and without affecting FLT3 phosphorylation or stability. The mechanism for ABL2-mediated negative regulation of FLT3 AKT signaling remains to be elucidated (Kazi et al, 2017; reviewed in Kazi and Ronnstrand, 2019).

Literature references

Kazi, JU., Sun, J., Shah, K., Chougule, RA., Gazi, M., Nagaraj, SR. et al. (2017). ABL2 suppresses FLT3-ITD-induced cell proliferation through negative regulation of AKT signaling. *Oncotarget, 8*, 12194-12202. ↗

Editions

2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

Table of Contents