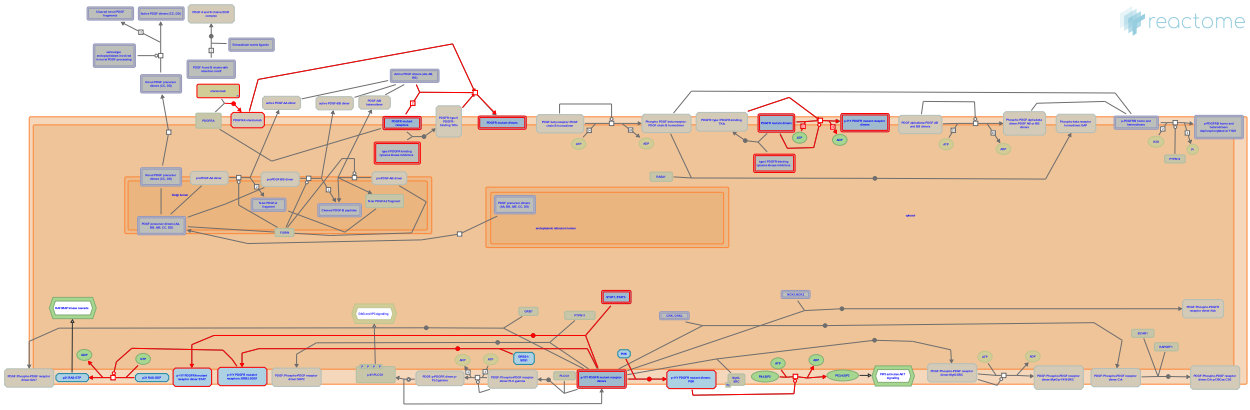
Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants



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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.

30/04/2024

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. ↗

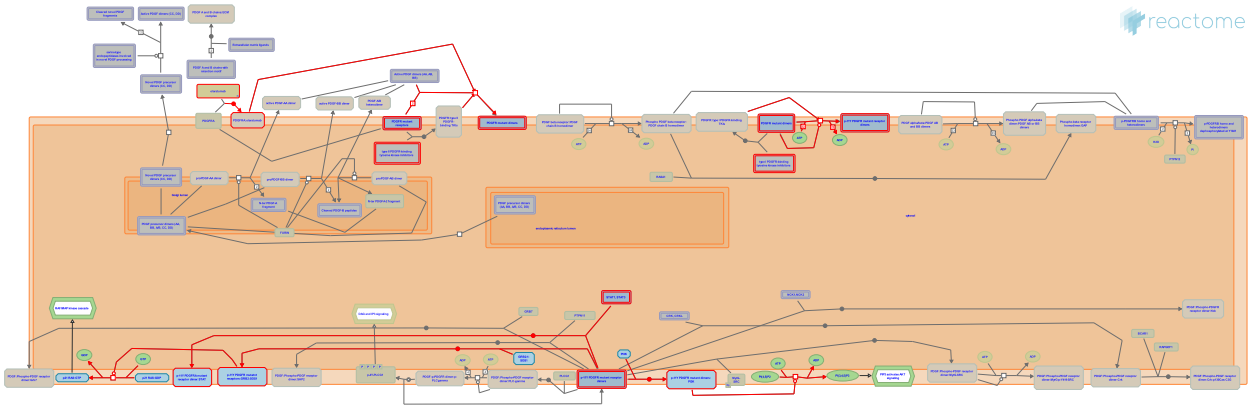
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

↗

Stable identifier: R-HSA-9673767

Diseases: cancer



PDGFRA is a type III transmembrane receptor tyrosine kinase. The extracellular domain consists of 5 immunoglobulin (IG) domains that contribute to dimerization and ligand binding. The intracellular region has a juxtamembrane domain that plays a role in autoinhibiting the receptor in the absence of ligand, and a bi-lobed kinase region with an activation loop and the catalytic cleft (reviewed in Klug et al, 2018). Upon ligand binding, PDGFRA undergoes dimerization and transautophosphorylation at at least 11 tyrosine residues in the intracellular domain. These phosphorylated residues are binding sites for downstream effectors of PDGFRA-responsive signaling pathways (reviewed in Klug et al, 2018; Roskoski, 2018).
PDGFRA is subject to activating mutations in a number of cancers, including gastrointestinal stromal tumors (GIST), melanoma and haematological cancers (reviewed in Corless et al, 2011; Wang et al, 2016; Roskoski, 2018). The most prevalent mutations in PDGFRA are at residue V561 in the juxtamembrane domain, N659 in the small lobe of the kinase domain and D842 in the activation loop of the kinase domain. PDGFRA is also subject to short deletions in the activation loop segment (reviewed in Roskoski, 2018). Acitvated forms of the protein may signal from the plasma membrane, similar to the wild type receptor, however there is also evidence that some mutants, notably D842V and V561D localize primarily to the Golgi membrane (Bahlawane et al, 2014). Activated PDGFRA mutants signal constitutively in the absence of ligand (reviewed in Roskoski, 2018; Wang et al, 2016; Klug et al, 2018).

Literature references

Yao, X., Chen, Y., Wu, M., Qian, H., Wang, Y., Wu, Y. et al. (2016). The platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are major players in oncogenesis, drug resistance, and attractive oncologic targets in cancer. *Growth Factors, 34*, 64-71. ↗

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

Roskoski, R. (2018). The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 129*, 65-83. ↗

Muller, A., Satagopam, VP., Girod, A., Sauter, T., Haan, S., Eulenfeld, R. et al. (2015). Constitutive activation of oncogenic PDGFRα-mutant proteins occurring in GIST patients induces receptor mislocalisation and alters PDGFRα signalling characteristics. *Cell Commun. Signal, 13*, 21. ↗

Heinrich, MC., Kent, JD., Klug, LR. (2018). Structural and clinical consequences of activation loop mutations in class III receptor tyrosine kinases. *Pharmacol. Ther., 191*, 123-134. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
2020-02-25	Authored, Edited	Rothfels, K.

Ligand-independent dimerization of PDGFR mutants ↗

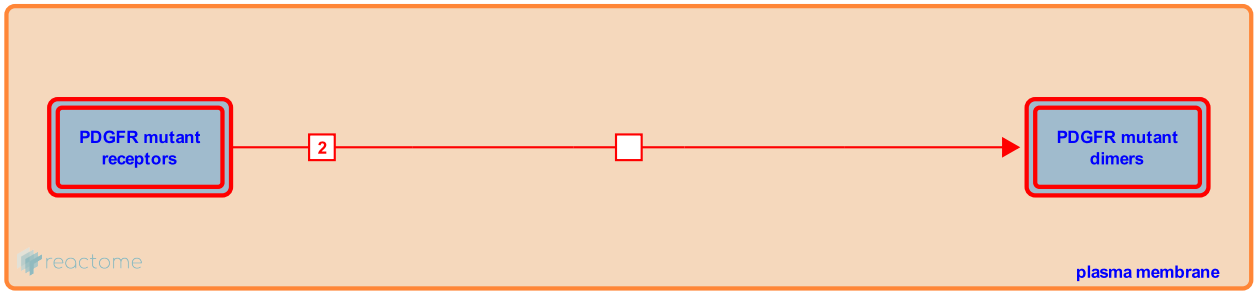
Location: Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

Stable identifier: R-HSA-9672168

Type: transition

Compartments: plasma membrane

Diseases: cancer



Activating missense and small in-frame deletion mutations in PDGFRA occur in some cancers, including KIT-mutant negative gastroinstestinal tumors (GIST) and haematological malignancies (Corless et al, 2005; Heinrich et al, 2003; Hirota et al, 2003; Poveda et al, 2017; reviewed in Roskoski, 2018; Klug et al, 2018). Mutations cluster in the autoinhibitory juxtamembrane domain or the kinase domain, but are also found at low frequency in the transmembrane domain (Heinrich et al, 2003; Corless et al, 2005; Velghe et al, 2014; Ip et al, 2018; reviewed in Klug et al, 2018). Most characterized gain-of-function PDGFRA mutants activate aberrant signaling by promoting ligand-independent dimerization and autophosphorylation (Heinrich et al, 2003; Corless et al, 2005; Velghe et al, 2014; reviewed in Klug et al, 2018).

Followed by: Autophosphorylation of PDGFR mutant dimers

Literature references

Vellano, CP., Scott, KL., Ju, Z., Jeong, KJ., Shao, SH., Leonard, PG. et al. (2018). Neomorphic PDGFRA extracellular domain driver mutations are resistant to PDGFRA targeted therapies. *Nat Commun, 9*, 4583. ↗

Roskoski, R. (2018). The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 129*, 65-83. ↗

Corless, CL., Heinrich, MC., Singer, S., Griffith, DJ., Town, A., Haley, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science, 299*, 708-10. ↗

Kitamura, Y., Shinomura, Y., Isozaki, K., Nishida, T., Kinoshita, K., Ohashi, A. et al. (2003). Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology, 125*, 660-7. ↗

Romero, I., Martín-Broto, J., López-Guerrero, JA., Grupo Español de Investigación en Sarcomas/Spanish Group for Sarcoma Research, -., Martínez, V., Valverde, C. et al. (2017). GEIS guidelines for gastrointestinal sarcomas (GIST). *Cancer Treat. Rev., 55*, 107-119. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
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Autophosphorylation of PDGFR mutant dimers ↗

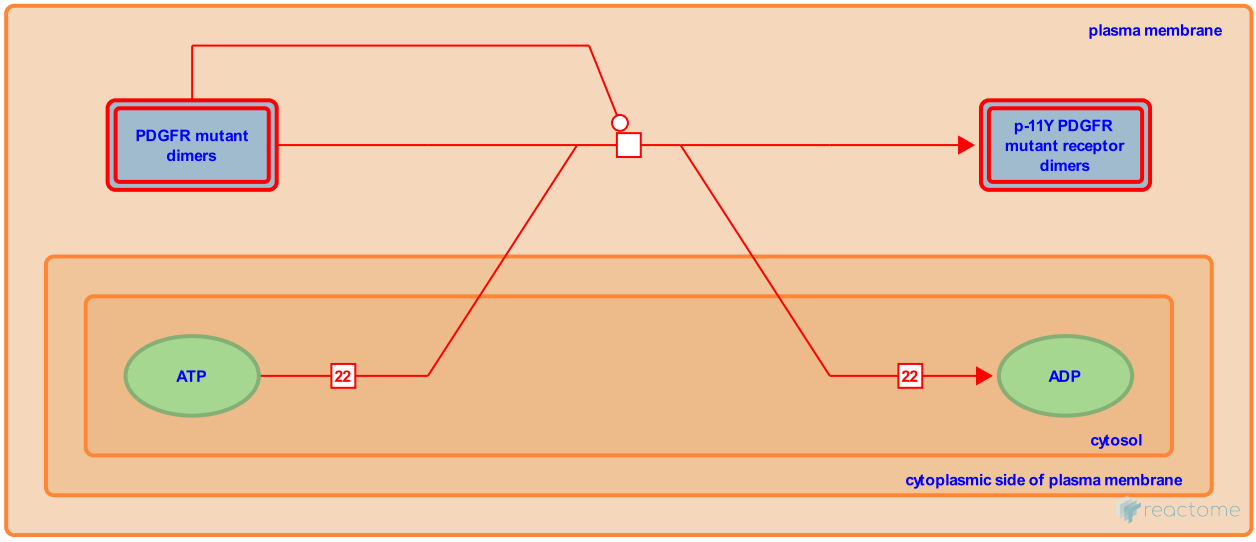
Location: Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

Stable identifier: R-HSA-9672175

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer



Activating mutations in the kinase, juxtamembrane and transmembrane domains of PDGFRA lead to constitutive, ligand-independent dimerization and trans-autophosphorylation, and stimulate downstream signaling pathways (Heinrich et al, 2003; Hirota et al, 2003; Corless et al, 2005; Velghe et al, 2014; reviewed in Roskoski et al, 2018; Klug et al, 2018).

Preceded by: Ligand-independent dimerization of PDGFR mutants

Followed by: GRB2:SOS1 complex binds to mutant PDGFR receptor, STAT binds to the mutant PDGFRA receptor, PI3-kinase binds to mutant PDGFR receptor

Literature references

Roskoski, R. (2018). The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 129*, 65-83. ↗

Corless, CL., Heinrich, MC., Singer, S., Griffith, DJ., Town, A., Haley, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science, 299*, 708-10. ↗

Kitamura, Y., Shinomura, Y., Isozaki, K., Nishida, T., Kinoshita, K., Ohashi, A. et al. (2003). Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology, 125*, 660-7. ↗

Heinrich, MC., Kent, JD., Klug, LR. (2018). Structural and clinical consequences of activation loop mutations in class III receptor tyrosine kinases. *Pharmacol. Ther., 191*, 123-134. ↗

Shiraga, S., McGreevey, L., Schroeder, A., Corless, CL., Heinrich, MC., Harrell, P. et al. (2005). PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J. Clin. Oncol., 23*, 5357-64. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
2020-02-25	Authored, Edited	Rothfels, K.

GRB2:SOS1 complex binds to mutant PDGFR receptor ↗

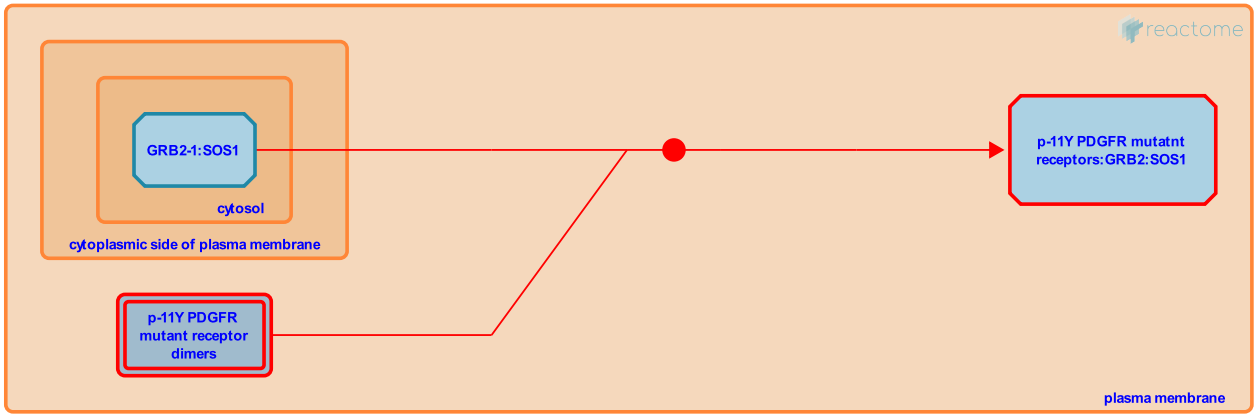
Location: Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

Stable identifier: R-HSA-9672164

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



MAP kinase signaling is activated downstream of gain-of-function missense and in-frame deletion PDGFRA mutants, as assessed by increased levels of phosphorylated MAPK3 and MAPK1 proteins (ERK1 and ERK2, respectively) (Heinrich et al, 2003; Corless et al, 2005; Ohashi et al, 2004; Velghe et al, 2014). RAS and MAPK activation is assumed to occur through the recruitment of GRB2:SOS1 to phosphorylated T720, as is the case for the wild-type receptor, although this has not been conclusively demonstrated (Bazenet et al, 1996; reviewed in Corless et al, 2011; Roskoski, 2018).

Preceded by: Autophosphorylation of PDGFR mutant dimers

Literature references

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

Roskoski, R. (2018). The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 129*, 65-83. ↗

Kitamura, Y., Shinomura, Y., Isozaki, K., Nishida, T., Kinoshita, K., Ohashi, A. et al. (2004). Different inhibitory effect of imatinib on phosphorylation of mitogen-activated protein kinase and Akt and on proliferation in cells expressing different types of mutant platelet-derived growth factor receptor-alpha. *Int. J. Cancer, 111*, 317-21. ↗

Corless, CL., Heinrich, MC., Singer, S., Griffith, DJ., Town, A., Haley, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science, 299*, 708-10. ↗

Shiraga, S., McGreevey, L., Schroeder, A., Corless, CL., Heinrich, MC., Harrell, P. et al. (2005). PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J. Clin. Oncol., 23*, 5357-64. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
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SOS-mediated nucleotide exchange of RAS downstream of mutant PDGFR receptors

↗

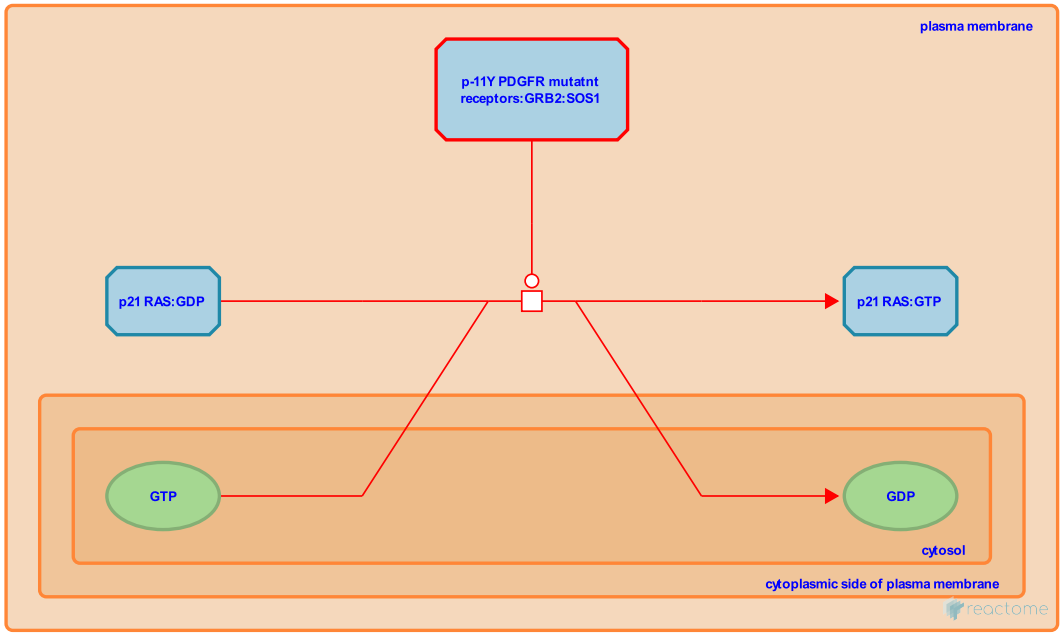
Location: Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

Stable identifier: R-HSA-9672170

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer



SOS-mediated exchange of GTP for GDP on RAS is predicted to be stimulated by gain-of-function PDGFRA mutants, based on the increased levels of phosphorylated MAPK3 and MAPK1 proteins (ERK1 and ERK2, respectively) (Heinrich et al, 2003; Corless et al, 2005; Ohashi et al, 2004; Velghe et al, 2014; reviewed in Corless et al, 2011; Roskoski, 2018).

Literature references

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

Roskoski, R. (2018). The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 129*, 65-83. ↗

Kitamura, Y., Shinomura, Y., Isozaki, K., Nishida, T., Kinoshita, K., Ohashi, A. et al. (2004). Different inhibitory effect of imatinib on phosphorylation of mitogen-activated protein kinase and Akt and on proliferation in cells expressing different types of mutant platelet-derived growth factor receptor-alpha. *Int. J. Cancer, 111*, 317-21. ↗

Corless, CL., Heinrich, MC., Singer, S., Griffith, DJ., Town, A., Haley, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science, 299*, 708-10. ↗

Shiraga, S., McGreevey, L., Schroeder, A., Corless, CL., Heinrich, MC., Harrell, P. et al. (2005). PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J. Clin. Oncol., 23*, 5357-64. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
2020-02-25	Authored, Edited	Rothfels, K.

PI3-kinase binds to mutant PDGFR receptor ↗

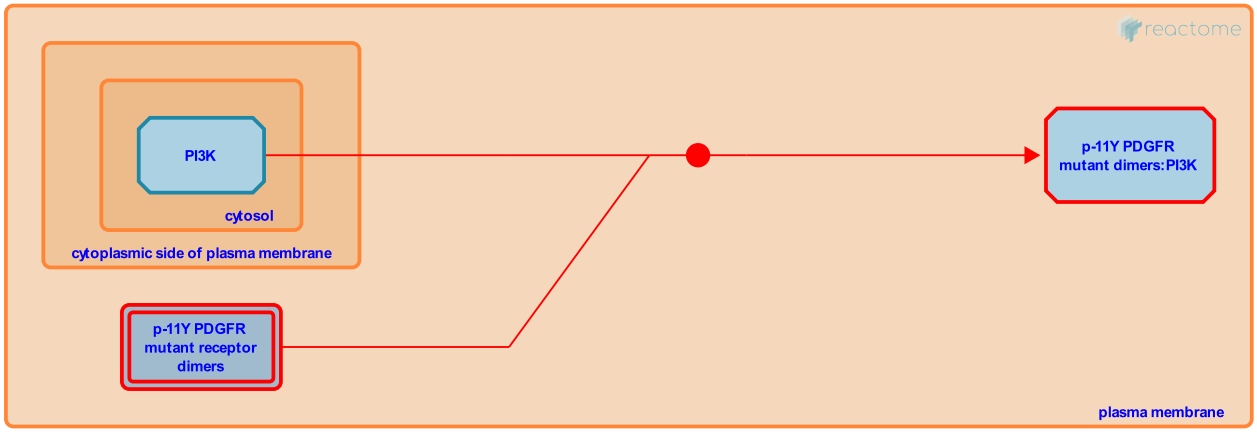
Location: Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

Stable identifier: R-HSA-9672172

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



Gain-of-function mutants of PDGFRA bind to phosphatidylinositol-3' kinase (PI3K) to activate AKT signaling, as assessed by the presence of phosphorylated AKT in Western blot analysis (Heinrich et al, 2003; Ohashi et al, 2004; reviewed in Corless et al, 2011). Interaction of PI3K with mutant PDGFRA receptors is assumed to occur through binding to phosphorylated Y731 and Y742 as is the case for the wild-type receptor, although this hasn't been directly demonstrated (reviewed in Roskoski, 2018).

Preceded by: Autophosphorylation of PDGFR mutant dimers

Followed by: PI3K catalyses the phosphorylation of PIP2 to PIP3 downstream of mutant PDGFR

Literature references

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

Roskoski, R. (2018). The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 129*, 65-83. ↗

Kitamura, Y., Shinomura, Y., Isozaki, K., Nishida, T., Kinoshita, K., Ohashi, A. et al. (2004). Different inhibitory effect of imatinib on phosphorylation of mitogen-activated protein kinase and Akt and on proliferation in cells expressing different types of mutant platelet-derived growth factor receptor-alpha. *Int. J. Cancer, 111*, 317-21. ↗

Corless, CL., Heinrich, MC., Singer, S., Griffith, DJ., Town, A., Haley, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science, 299*, 708-10. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
2020-02-25	Authored, Edited	Rothfels, K.

PI3K catalyses the phosphorylation of PIP2 to PIP3 downstream of mutant PDGFR ↗

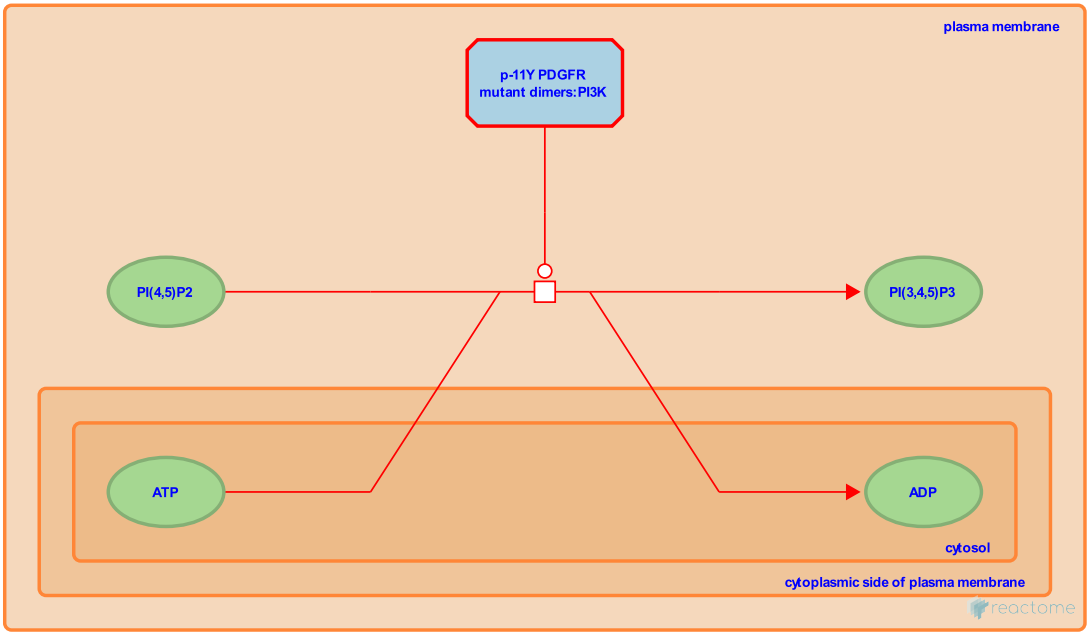
Location: Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

Stable identifier: R-HSA-9672177

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer



PI3K/AKT signaling is initiated downstream of PDGFRA gain-of-function missense and in-frame deletion mutants as assessed by the presence of phosphorylated AKT in Western blot analysis (Heinrich et al, 2003; Osashi et al, 2005; Bahlawane et al, 2015; Paugh et al, 2013; reviewed in Corless et al, 2011).

Preceded by: PI3-kinase binds to mutant PDGFR receptor

Literature references

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

Kitamura, Y., Shinomura, Y., Isozaki, K., Nishida, T., Kinoshita, K., Ohashi, A. et al. (2004). Different inhibitory effect of imatinib on phosphorylation of mitogen-activated protein kinase and Akt and on proliferation in cells expressing different types of mutant platelet-derived growth factor receptor-alpha. *Int. J. Cancer, 111*, 317-21. ↗

Corless, CL., Heinrich, MC., Singer, S., Griffith, DJ., Town, A., Haley, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science, 299*, 708-10. ↗

Muller, A., Satagopam, VP., Girod, A., Sauter, T., Haan, S., Eulenfeld, R. et al. (2015). Constitutive activation of oncogenic PDGFRα-mutant proteins occurring in GIST patients induces receptor mislocalisation and alters PDGFRα signalling characteristics. *Cell Commun. Signal, 13*, 21. ↗

Diaz, AK., Zhang, J., Broniscer, A., Zhang, J., Zhu, X., Baker, SJ. et al. (2013). Novel oncogenic PDGFRA mutations in pediatric high-grade gliomas. *Cancer Res., 73*, 6219-29. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
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STAT binds to the mutant PDGFRA receptor ↗

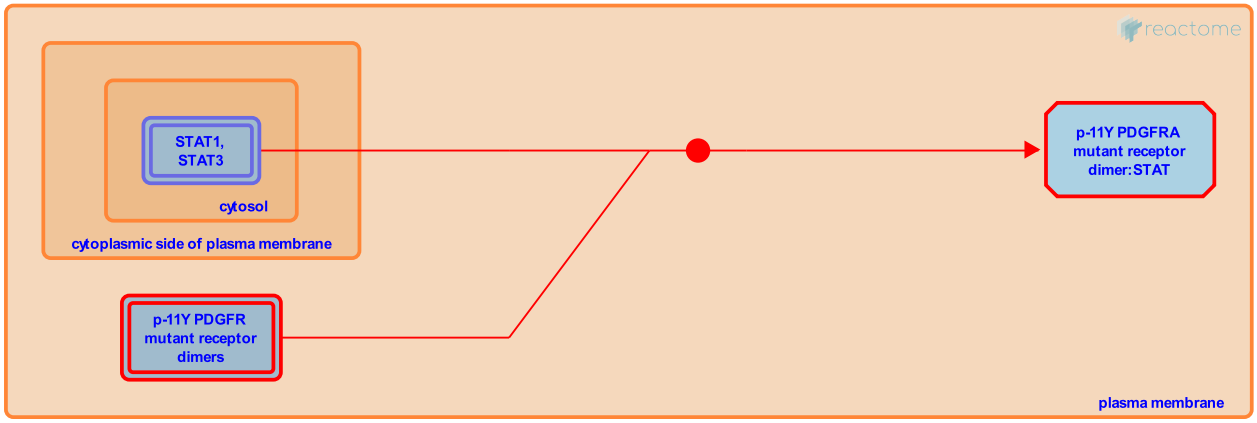
Location: Signaling by PDGFRA transmembrane, juxtamembrane and kinase domain mutants

Stable identifier: R-HSA-9672176

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



Like the WT receptor, gain-of-function missense and in-frame deletion mutants of PDGFRA appear to act through the STAT signaling pathway. Binding and phosphorylation of SRC and subsequently STAT1 and 3 has been demonstrated for the activation loop D842V mutant, the juxtamembrane domain V561D mutant and for a small number of short in-frame deletion mutants in the kinase and juxtamembrane domain region. Specificity for interaction with different STAT family members is likely to vary depending on the PDGFRA mutation (Heinrich et al, 2003; Velghe et al, 2014; reviewed in Klug et al, 2018; Wang et al, 2016; Corless et al, 2011).

Preceded by: Autophosphorylation of PDGFR mutant dimers

Literature references

Yao, X., Chen, Y., Wu, M., Qian, H., Wang, Y., Wu, Y. et al. (2016). The platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are major players in oncogenesis, drug resistance, and attractive oncologic targets in cancer. *Growth Factors, 34*, 64-71. ↗

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Corless, CL., Heinrich, MC., Singer, S., Griffith, DJ., Town, A., Haley, A. et al. (2003). PDGFRA activating mutations in gastrointestinal stromal tumors. *Science, 299*, 708-10. ↗

Heinrich, MC., Kent, JD., Klug, LR. (2018). Structural and clinical consequences of activation loop mutations in class III receptor tyrosine kinases. *Pharmacol. Ther., 191*, 123-134. ↗

Polyansky, AA., Hallberg, B., Van Cauwenberghe, S., Demoulin, JB., Montano-Almendras, CP., Chand, D. et al. (2014). PDGFRA alterations in cancer: characterization of a gain-of-function V536E transmembrane mutant as well as loss-of-function and passenger mutations. *Oncogene, 33*, 2568-76. ↗

Editions

2020-02-06	Reviewed	Ip, CKM.
2020-02-25	Authored, Edited	Rothfels, K.

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