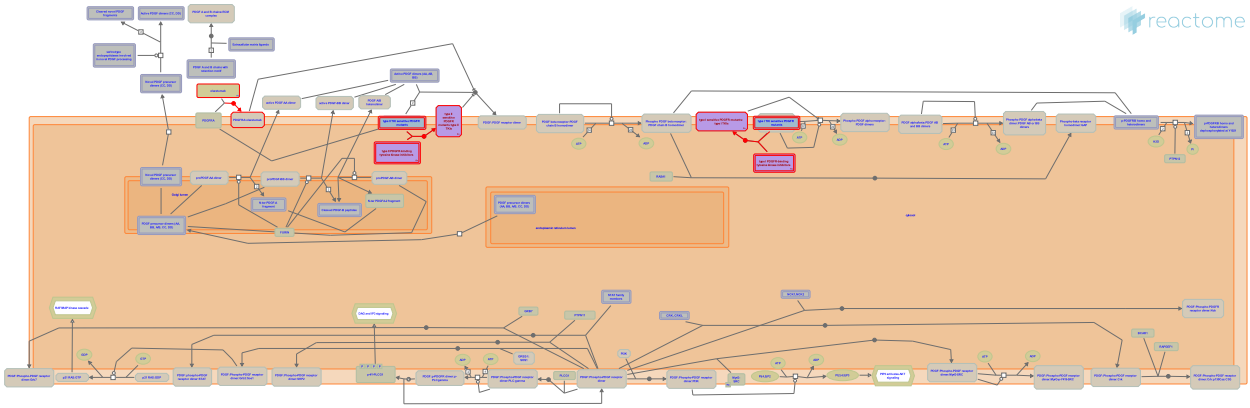
PDGFR mutants bind TKIs



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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.

01/05/2024

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. ↗

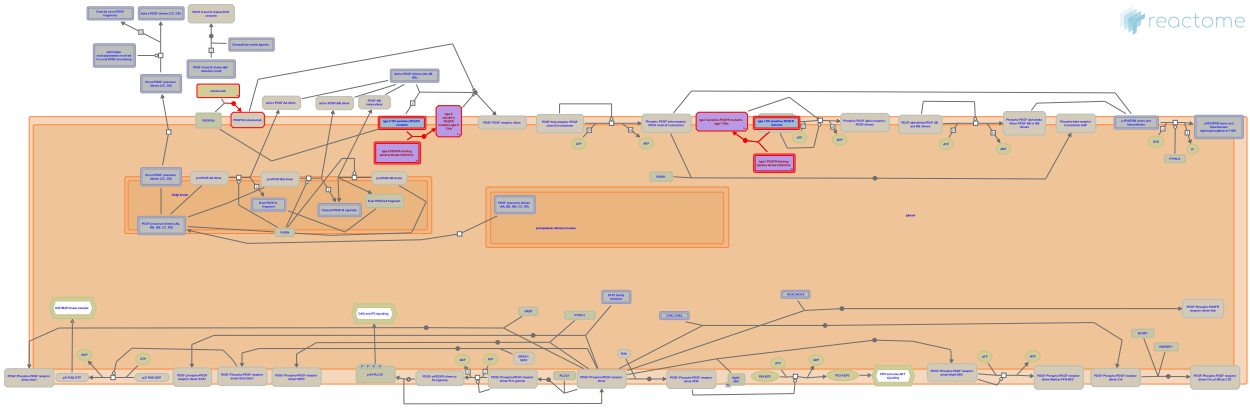
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

PDGFR mutants bind TKIs ↗

Stable identifier: R-HSA-9674428

Diseases: cancer



Aberrant signaling by activated forms of PDGFR can be inhibited by tyrosine kinase inhibitors (TKIs). PDGF receptors are class III receptor tyrosine kinase receptors, also known as dual-switch. Dual-switch receptors are activated through a series of phosphorylation and conformational changes that move the receptor from the inactive form to the fully activated form. Type II TKIs bind to the inactive form of the receptor at a site adjacent to the ATP-binding cleft, while type I TKIs bind to the active form (reviewed in Roskoski, 2018; Klug et al, 2018).

Primary mutations in PDGRFA occur in the activation loop, with a minor fraction found in the juxtamembrane domain (reviewed in Roskoski, 2018; Klug et al, 2018). Juxtamembrane domain mutations affect an autoinhibitory loop, shifting the equilibrium of the receptor towards the activated state; despite this, however, juxtamembrane domain mutants remain predominantly in the inactive state and as such are susceptible to inhibition by type II TKIs. Activation loop mutations more strongly favor the active conformation of the receptor and are susceptible to inhibition by both type II and type I TKI. The most prevalent PDGFRA mutation, D842V, promotes the active conformation strongly enough to be resistant to type II TKIs (reviewed in Roskoski, 2018; Klug et al, 2018).

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. ↗

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

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PDGFR mutants bind type II TKIs ↗

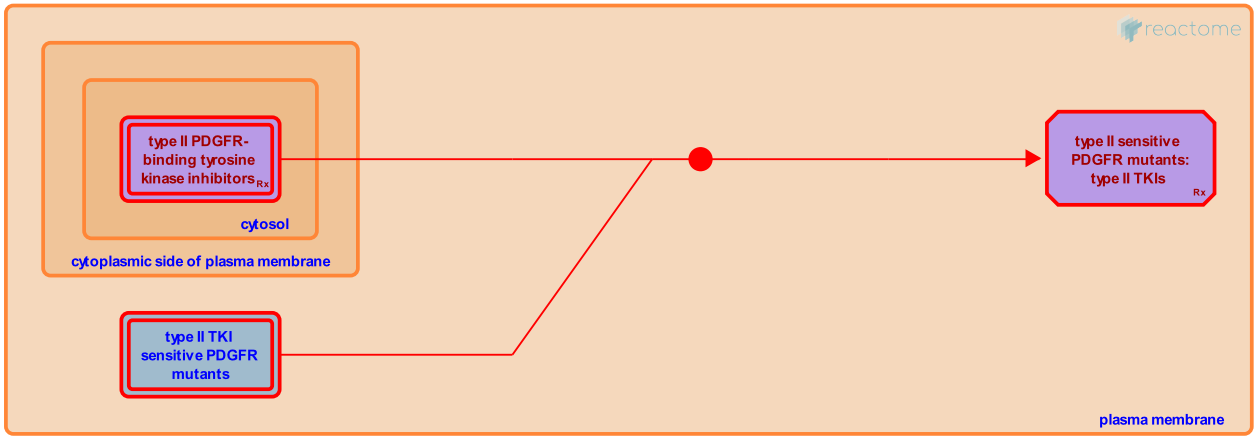
Location: PDGFR mutants bind TKIs

Stable identifier: R-HSA-9674430

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



Imatinib and other type II tyrosine kinase inhibitors bind to the inactive conformation of the PDGF receptors at site near the ATP-binding site that is not present in the active conformation (reviewed in Klug et al, 2018). Juxtamembrane domain mutants of PDGFRA such as V561D relieve the autoinhibition of the receptor without completely driving the equilibrium to the fully active form; as a result, juxtamembrane mutants tend to be sensitive to type II TKIs. Mutations in the activation loop, in contrast, much more strongly shift the equilibrium of the protein toward the active state, and mutations in this region, such as the most prevalent D842V, tend to be resistant to type II TKIs (reviewed in Roskoski, 2018; Klug et al, 2018)

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. ↗

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. ↗

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PDGFR mutants bind type I TKIs ↗

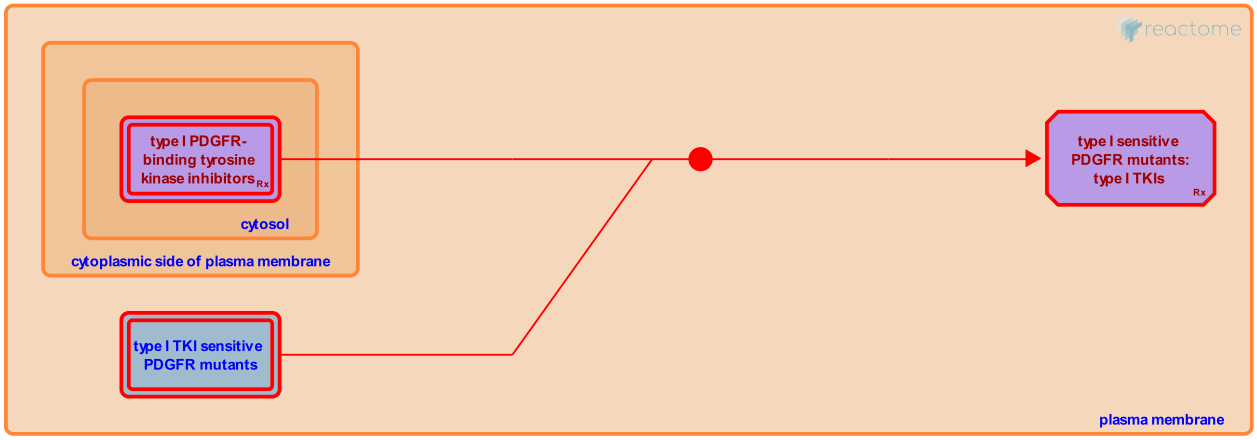
Location: PDGFR mutants bind TKIs

Stable identifier: R-HSA-9674427

Type: binding

Compartments: plasma membrane, cytosol

Diseases: cancer



Avipritinib, crenolanib, pazopanib and other type I tyrosine kinase inhibitors bind to the active form of the PDGF receptors and prevent their trans-autophosphorylation (reviewed in Roskoski, 2018; Klug et al, 2018; Papadopoulos and Lennartsson, 2016). PDGFRA receptors with mutations that strongly promote the active state, such as mutations in the kinase domain or the gatekeeper mutation T674I tend to be sensitive to type I TKIs. In contrast, the extracellular domain mutation Y288C is resistant to type I TKIs (Ip et al, 2018; reviewed in Roskoski, 2018; Klug et al, 2018).

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. ↗

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. ↗

Lennartsson, J., Papadopoulos, N. (2018). The PDGF/PDGFR pathway as a drug target. *Mol. Aspects Med., 62*, 75-88. ↗

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