Ligand-independent dimerization of PDG-FR mutants

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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.

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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. ↗

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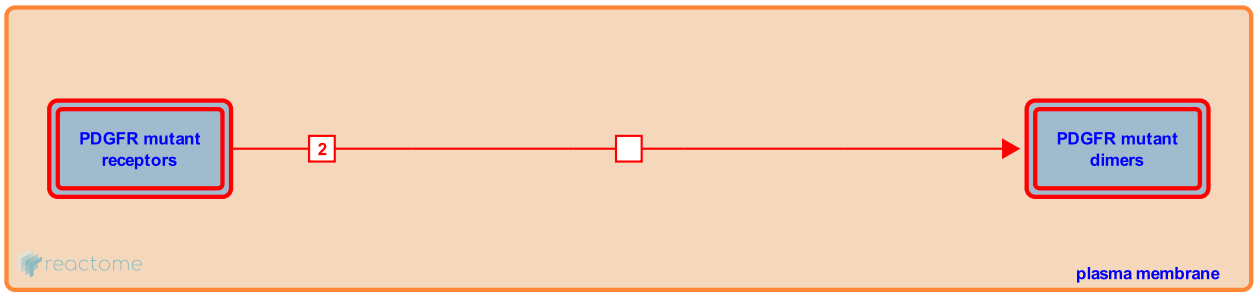
Stable identifier: R-HSA-9672168

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).

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

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