Signaling by PDGF

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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.

17/11/2022
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


Reactome database release: 82

This document contains 2 pathways and 15 reactions (see Table of Contents)
Platelet-derived Growth Factor (PDGF) is a potent stimulator of growth and motility of connective tissue cells such as fibroblasts and smooth muscle cells as well as other cells such as capillary endothelial cells and neurons. The PDGF family of growth factors is composed of four different polypeptide chains encoded by four different genes. The classical PDGF chains, PDGF-A and PDGF-B, and more recently discovered PDGF-C and PDGF-D. The four PDGF chains assemble into disulphide-bonded dimers via homo- or heterodimerization, and five different dimeric isoforms have been described so far; PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD. It is notable that no heterodimers involving PDGF-C and PDGF-D chains have been described. PDGF exerts its effects by binding to, and activating, two protein tyrosine kinase (PTK) receptors, alpha and beta. These receptors dimerize and undergo autophosphorylation. The phosphorylation sites then attract downstream effectors to transduct the signal into the cell.

**Literature references**


**Editions**

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All the newly synthesized PDGF chains are dimerized in the ER and thereafter transferred to the Golgi complex for proteolytic processing. The four PDGF chains assemble into disulphide-bonded dimers via homo- or heterodimerization, and five different dimeric isoforms have been described so far; PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD.

Followed by: Release of novel PDGFs as latent factors, PDGF-BB cleavage by Furin, PDGF-AB cleavage by Furin, PDGF-AA cleavage by Furin

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After dimerization of the PDGF-A and PDGF-B chains in the ER of producing cells, the dimers are proteolytically cleaved in the trans-Golgi network during protein maturation and secretion. The dibasic-specific proprotein convertase, furin, or related convertases are involved in the conversion of proPDGF forms to active PDGF forms. PDGF-A chains are expressed as two different isoforms, a longer and a shorter form. The longer (241 aa) is less common and differs from the shorter one (196 aa) by a C-terminal extension of 18 aa (Beckmann et al. 1988, Ostman et al. 1992). The PDGF-A chains are cleaved singly at the RRRKR sequence at 86 position to yield predominantly, the secreted PDGF-AA forms, while PDGF-BB are reported that at least three forms of PDGF-BB can be formed (Seidah & Prat 2002). This includes an approx 24 kDa form retained intracellularly and degraded in lysosomes, a secreted approx 30 kDa form and an approx 40 kDa cell surface-associated form. PDGF-B is processed at the 'RGRR' sequence at position 81 and a second cleavage close to residues 'ARPVT' at position 190 (Siegfried et al. 2005, Ostman et al. 1992, Heldin & Westermark 1999).

**Preceded by:** Translocation of PDGF from ER to Golgi

**Followed by:** PDGF binds to extracellular matrix proteins, PDGF dimer binds two receptors simultaneously

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**Preceded by:** Translocation of PDGF from ER to Golgi

**Followed by:** PDGF dimer binds two receptors simultaneously

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**Release of novel PDGFs as latent factors**

**Location:** Signaling by PDGF

**Stable identifier:** R-HSA-382057

**Type:** omitted

**Compartments:** Golgi membrane, extracellular region

Novel PDGFs both PDGF-CC and PDGF-DD dimers are secreted as latent factors without removal of the N-terminal CUB domain. These require further activation by extracellular proteolysis.

**Preceded by:** Translocation of PDGF from ER to Golgi

**Followed by:** Extracellular processing of novel PDGFs

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During the extracellular proteolytic activation of PDGF-C and PDGF-D chains, the CUB domains is removed and plasmin protease has been shown to proteolytically cleave within the hinge regions, and thus releasing the corresponding growth factor domains. In addition the protease tissue-type plasminogen activator (tPA) is also involved in the activation of PDGF-CC but not able to cleave and activate PDGF-DD.

**Preceded by:** Release of novel PDGFs as latent factors

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PDGF binds to extracellular matrix proteins

Location: Signaling by PDGF

Stable identifier: R-HSA-382054

Type: binding

Compartments: extracellular region

The long splice version of the PDGF-A chain as well as the COOH-terminal part of the PDGF-B precursor contain C-terminal protein motifs that confer retention of the secreted factors. In both the PDGF A- and B-chains, exon 6 encodes a basic sequence that mediates interaction with components of the extracellular matrix. PDGF binds to various types of collagens, thrombospondin and osteopontin; however, the major component of the matrix involved in PDGF binding is likely to be haparan sulphate. The negatively charged sulfate groups on the disaccharide building blocks of heparan sulfate (HS) polysaccharide chains provide binding sites for positively charged amino acid sequence motifs.

The precursor of the B-chain may be retained in the matrix; after maturation when the COOH-terminal retention sequence has been cleaved off, the molecule may become more diffusible.

Preceded by: PDGF-AA cleavage by Furin

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PDGF dimer binds two receptors simultaneously

Location: Signaling by PDGF

Stable identifier: R-HSA-186773

Type: omitted

Compartments: plasma membrane

PDGF dimer binds two receptors simultaneously. The receptors dimerise on ligand binding and undergo conformational change which is key to receptor autophosphorylation (reviewed in Heldin et al, 1998). PDGFRA and PDGFRB activity can be inhibited by binding to type I and type II tyrosine kinase inhibitors (reviewed in Roskoski, 2018). Type I inhibitors such as crenolanib, avripatinib and pazopanib, bind to the active conformation of the receptor, while type II inhibitors like imatinib, sorafenib and others bind to the inactive conformation (Gril et al, 2013; Wang et al, 2014; Mathias et al, 2015; Meliau et al, 2017; Lombardo et al, 2004; Chen et al, 2006; Matsui et al, 2008; Liu et al, 2011; Hilberg et al, 2008; Hilberg et al, 2017; Wilhelm et al, 2002; Strumberg et al, 2005; Mendel et al, 2003; Roskoski, 2007). PDGFRA signaling can also be inhibited by the monoclonal antibody olaratumab, which interferes with binding of AA, BB and CC ligand to the receptor (Gerber et al, 2012; Loizos et al, 2005; Matei et al, 2006; Russell et al, 2010; Stock et al, 2007).

Preceded by: PDGF-AA cleavage by Furin, PDGF-AB cleavage by Furin, PDGF-BB cleavage by Furin

Followed by: Autophosphorylation of PDGF beta receptors, Autophosphorylation of PDGF alpha/beta receptors, Autophosphorylation of PDGF alpha receptors

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Sensi, E., Cipollini, M., Cristaudo, A., Guazzelli, A., Catalano, C., Meliau, O. et al. (2017). Inhibition of the platelet-derived growth factor receptor beta (PDGFRB) using gene silencing, crenolanib besylate, or imatinib mesylate hampers the malignant phenotype of mesothelioma cell lines. Genes Cancer, 8, 438-452.


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Autophosphorylation of PDGF beta receptors

Location: Signaling by PDGF

Stable identifier: R-HSA-186786

Type: transition

Compartments: plasma membrane, cytosol

Receptor dimerisation is key event in PDGF receptor activation. The intracellular regions of the receptors are juxtaposed which allows trans-phosphorylation between the two receptors in the complex.

The autophosphorylation site Y857 located inside the kinase domain of beta-receptor (PDGFRB) is important for activation of the kinase. This tyrosine is conserved in the alpha-receptor (PDGFRA), where it corresponds to Y849, and in almost all other tyrosine kinase receptors. The other known autophosphorylation sites are located outside the kinase domains of the alpha- and beta- receptors; of the 15 (beta) or 16 (alpha) tyrosine residues in the intracellular, non-catalytic part of the beta- or alpha receptor, 11 and 10, respectively, are autophosphorylation sites (reviewed in Heldin et al, 1998).

PDGFRA and PDGFRB activity can be inhibited by binding to type I and type II tyrosine kinase inhibitors (reviewed in Roskoski, 2018). Type I inhibitors such as crenolanib, avripatinib and pazopanib, bind to the active conformation of the receptor and inhibit trans-autophosphorylation (Ip et al, 2018; Evans et al, 2017; Davids et al, 2009; reviewed in Roskoski, 2018; Klug et al, 2018; Papadopoulos and Lennartsson, 2016).

Preceded by: PDGF dimer binds two receptors simultaneously

Followed by: PTPN12 dephosphorylates PDGFRB at Y1021

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Preceded by: PDGF dimer binds two receptors simultaneously

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Preceded by: PDGF dimer binds two receptors simultaneously

Followed by: PTPN12 dephosphorylates PDGFRB at Y1021

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The role of autophosphorylation sites on PDGF receptors are to provide docking sites for downstream signal transduction molecules which contain SH2 domains. The SH2 domain is a conserved motif of around 100 amino acids that can bind a phosphorylated tyrosine residue. These downstream molecules are activated upon binding to, or phosphorylated by, the receptor kinases intrinsic to PDGF receptors.

Some of the downstream molecules are themselves enzymes, such as phosphatidylinositol 3'-kinase (PI3K), phospholipase C (PLC-gamma), the Src family of tyrosine kinases, the tyrosine phosphatase SHP2, and a GTPase activating protein (GAP) for Ras. Others such as Grb2 are adaptor molecules which link the receptor with downstream catalytic molecules.

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Protein tyrosine phosphatase PTPN12 dephosphorylates activated PDGFRB (PDGF receptor beta) at tyrosine residue Y1021, which contributes to the tumor suppressor role of PTPN12 in triple negative breast cancer in addition to PTPN12-mediated dephosphorylation of ERBB2 (HER2) at Y1248 (Sun et al. 2011).

**Preceded by:** Autophosphorylation of PDGF alpha/beta receptors, Autophosphorylation of PDGF beta receptors

**Literature references**
Olaratumab binds PDGFRA

Location: Signaling by PDGF

Stable identifier: R-HSA-9674015

Type: binding

Compartments: plasma membrane

Diseases: cancer

Olaratumab is an anti-PDGFRA specific monoclonal antibody that blocks the binding of PDGF-AA, PDGF-BB and PDGF-CC (Loizos et al, 2005). Olaratumab inhibits proliferation of a number of tumor cell lines and is approved for treatment of soft tissue sarcoma (Gerber et al, 2012; Loizos et al, 2005; Matei et al, 2006; Russell et al, 2010; Stock et al, 2007).

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Wild-type PDGFRα and PDGFRβ can be bound and inhibited by class I tyrosine kinase inhibitors including pazopanib, avapritinib, and crenolanib (Gril et al, 2013; Wang et al, 2014; Mathias et al, 2015; Meliau et al, 2017; reviewed in Klug et al, 2018). Type I inhibitors bind in the ATP binding site of the active conformation and prevent full activation of the kinase (reviewed in Roskoski, 2018).

**Literature references**


Natarajan, K., Ambudkar, SV., Doshi, KA., Shukla, S., Mathias, TJ., Baer, MR. et al. (2015). The FLT3 and PDGFR inhibitor crenolanib is a substrate of the multidrug resistance protein ABCB1 but does not inhibit transport function at pharmacologically relevant concentrations. *Invest New Drugs*, 33, 300-9.


Wild-type PDGFRA and PDGFRB can be bound and inhibited by class II tyrosine kinase inhibitors including imatinib, nilotinib, sorafenib, sunitinib, ripretinib and others (Lombardo et al, 2004; Chen et la, 2006; Matsui et al, 2008; Liu et al, 2011; Hilberg et al, 2008; Hilberg et al 2017; Wilhelm et al 2002; Strumberg et al, 2005; Mendel et al, 2003; Roskoski, 2007; Smith et al, 2019). Type II inhibitors bind to the inactive conformation of the kinase and prevent its activation (reviewed in Roskoski, 2018; Papadopoulos and Lennartsson, 2018).

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