

## PDGFRs

### Key References

Claesson-Welsh, L., et al., cDNA cloning and expression of the human A-type platelet-derived growth factor (PDGF) receptor establishes structural similarity to the B-type PDGF receptor., *Proc. Natl. Acad. Sci. USA*, **86**, 4917-4921 (1989).

Heldin, C-H., ed., Thematic issue on platelet-derived growth factor., In *Cytokine & Growth Factor Reviews*, Volume **15**, 195-289 (2004).

Heldin, C-H. and Westermark, B., Mechanism of action and *in vivo* role of platelet-derived growth factor., *Physiol. Rev.*, **79**, 1283-1316 (1999).

Jayson, G.C., et al., Blockade of platelet-derived growth factor receptor- $\beta$  by CDP860, a humanized, PEGylated di-Fab', leads to fluid accumulation and is associated with increased tumor vascularized volume., *J. Clin. Oncol.*, **23**, 973-981 (2005).

Kazlauskas, A. and Cooper, J.A., Autophosphorylation of the PDGF receptor in the kinase insert region regulates interactions with cell proteins., *Cell*, **58**, 1121-1133 (1989).

Klinghoffer, R.A., et al., The two PDGF receptors maintain conserved signaling *in vivo* despite divergent embryological functions., *Mol. Cell*, **7**, 343-354 (2001).

Matsui, T., et al., Isolation of a novel receptor cDNA establishes the existence of two PDGF receptor genes., *Science*, **243**, 800-803 (1989).

Pietras, K., et al., PDGF receptors as cancer drug targets., *Cancer Cell*, **3**, 439-443 (2003).

Soriano, P., Abnormal kidney development and hematological disorders in PDGF  $\beta$ -receptor mutant mice., *Genes Dev.*, **8**, 1888-1896 (1994).

Soriano, P., The PDGF $\alpha$  receptor is required for neural crest cell development and for normal patterning of the somites., *Development*, **124**, 2691-2700 (1997).

Sundaresan, M., et al., Requirement for generation of H<sub>2</sub>O<sub>2</sub> for platelet-derived growth factor signal transduction., *Science*, **270**, 296-299 (1995).

Yarden, Y., et al., Structure of the receptor for platelet-derived growth factor helps define a family of closely related growth factor receptors., *Nature*, **323**, 226-232 (1986).

### Overview

Platelet-derived growth factor (PDGF) is a family of disulfide-bonded dimeric molecules of A-, B-, C- and D-polypeptide chains (PDGF-AA, -AB, -BB, -CC and -DD). PDGF isoforms stimulate proliferation, survival and motility of connective tissue cells, and certain other cell types.

PDGFs have important roles during the embryonal development to stimulate the differentiation and proliferation of specific mesenchymal cell types in different organs, such as smooth muscle cells and pericytes of blood vessels, mesangial cells in the kidney, alveolar myofibroblasts of the lung, and glial cells of the central nervous system. In the adult, PDGF is important for wound healing and for the regulation of the interstitial fluid pressure of tissues. Overactivity of PDGF is associated with malignancies, and other diseases characterized by excessive cell proliferation, including atherosclerosis and fibrotic conditions.

The cellular effects of PDGF are mediated by  $\alpha$ - and  $\beta$ -tyrosine kinase receptors. Each receptor contains five extracellular Ig-like domains and an intracellular kinase domain which contains an inserted sequence of about 100 amino acid residues without similarity to kinases. The PDGF chains bind the receptors with different specificities. Thus, the  $\alpha$ -receptor binds A-, B- and C-chains, whereas the  $\beta$ -receptor binds B- and D-chains. Ligand binding induces receptor dimerization; depending on the stimulating isoform,  $\alpha\alpha$ -homodimers,  $\beta\beta$ -homodimers or  $\alpha\beta$ -heterodimers are formed. Within the dimers, the receptors are autophosphorylated *in trans*, which has two important functions: Autophosphorylation of a conserved tyrosine residue in the activation loop of the kinase domain causes activation of

the kinase, and autophosphorylation of a number of tyrosine residues outside the kinase domain creates binding sites for downstream SH2 domain-containing molecules; the binding and activation of such molecules initiates a number of signaling pathways which leads to cell growth, survival and migration.

More than 10 families of SH2 domain proteins bind to the  $\alpha$ - and  $\beta$ -receptors. They are of different kinds, i.e. molecules with associated enzymatic activities which are activated and/or attracted to the inner leaflet of the cell membrane by the receptors, members of the Stat family of transcription factors which after activation are translocated to the nucleus where they effect transcription of specific genes, and adaptor molecules which mediate interactions with other signaling components. Examples of enzymes activated by PDGF receptors are the tyrosine kinase Src, phospholipase C- $\gamma$  (PLC- $\gamma$ ), phosphatidylinositol-3'-kinase (PI3K), GTPase activating protein (GAP) for Ras, and the tyrosine phosphatase SHP-2. Examples of adaptors include Shc, Nck, Grb2, Grb7 and Crk. Transient inhibition of tyrosine phosphatases through PI3K-dependent production of H<sub>2</sub>O<sub>2</sub> delays dephosphorylation and enhances the signals.

The  $\alpha$ - and  $\beta$ -receptors have overlapping but distinct signaling capacities, which are mainly dictated by which SH2-domain molecules they bind. Thus, both receptors stimulate cell growth, but whereas the  $\beta$ -receptor potently stimulates chemotaxis, the  $\alpha$ -receptor inhibits chemotaxis in certain cell types. *In vivo* experiments in mice, in which the cytoplasmic domains between the  $\alpha$ - and  $\beta$ -receptors were swapped, revealed that the  $\beta$ -receptor intracellular domain can fully substitute for

the  $\alpha$ -receptors. However, replacement of the  $\beta$ -receptors cytoplasmic domain with that of the  $\alpha$ -receptor causes abnormalities in vascular smooth muscle cell development and function.

There are examples that overactivity of PDGF receptors through enhanced autocrine ligand stimulation contributes to malignancies, e.g. dermatofibrosarcoma protuberans, in which the PDGF B-chain gene is fused to a collagen gene leading to the production of a fusion protein which is processed to PDGF-BB. There are also examples of activation of PDGF receptors by mutation in certain tumor types. Thus, translocation of the genes for PDGF  $\alpha$ - or  $\beta$ -receptors occur in hypereosinophilic syndrome and atypic chronic myeloid leukemias. In these cases, fusion proteins are formed between the kinase domains of the receptors and other molecules which cause constitutive dimerization and activation of the kinases. In a subfraction of gastrointestinal stromal tumors, the activation loop of the  $\alpha$ -receptor is mutated, and in a subfraction of glioblastoma multiforme, the  $\alpha$ -receptor gene is amplified. In each one of these cases the overactive receptor causes constitutive growth and survival signals which contribute to malignant transformation. Treatment of patients with certain of these diseases with selective PDGF receptor tyrosine kinase inhibitors, has given promising results.

## PDGFRs

FAMILY MEMBERS	PDGFR- $\alpha$	PDGFR- $\beta$
OTHER NAMES	—	CD140b
MOLECULAR WEIGHT/ STRUCTURAL DATA	170 kDa, 1098 aa	190 kDa, 1106 aa
ISOFORMS	Not known	Not known
SPECIES	All vertebrates	All vertebrates
DOMAIN ORGANIZATION	Transmembrane domain, 5 Ig-like domains extracellularly and a split tyrosine kinase domain intracellularly	Transmembrane domain 5 Ig-like domains extracellularly and a split tyrosine kinase domain intracellularly
PHOSPHORYLATION SITES	Tyr <sup>572</sup> , Tyr <sup>574</sup> , Tyr <sup>720</sup> , Tyr <sup>731</sup> , Tyr <sup>742</sup> , Tyr <sup>754</sup> , Tyr <sup>762</sup> , Tyr <sup>768</sup> , Tyr <sup>849</sup> , Tyr <sup>988</sup> , Tyr <sup>1018</sup>	Tyr <sup>579</sup> , Tyr <sup>581</sup> , Tyr <sup>716</sup> , Tyr <sup>740</sup> , Tyr <sup>751</sup> , Tyr <sup>763</sup> , Tyr <sup>771</sup> , Tyr <sup>775</sup> , Tyr <sup>778</sup> , Tyr <sup>857</sup> , Tyr <sup>1009</sup> , Tyr <sup>1021</sup>
TISSUE DISTRIBUTION	Fibroblasts, smooth muscle cells, glial cells	Fibroblasts, smooth muscle cells, pericytes
SUBCELLULAR LOCALIZATION	Plasma membrane	Plasma membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	SH2BPSM1, SHP-2, Cbl, PLC- $\gamma$ , Src family kinase, Shc, PI3K, Crk	SHP-2, PTP1c, RasGAP, Cbl, PI3K, PLC $\gamma$ , Nck, Shb, Grb7, STAT, Src family kinases, Shc, Grb2/Sos
UPSTREAM ACTIVATORS	PDGF-AA <sup>a</sup> , -AB <sup>a</sup> , -BB <sup>a</sup> , -CC <sup>a</sup>	PDGF-BB <sup>a</sup> , -DD <sup>a</sup>
DOWNSTREAM ACTIVATION	PI3K, PLC- $\gamma$ , Grb2/Sos, SHP-2, Src family kinases, Shc, Crk	SHP-2, PTP1c, RasGAP, c-cbl, p558, p85a, PLC $\gamma$ , Nck, Shb, Grb7, STAT, Src family kinases, Shc, Grb2/Sos
ACTIVATORS	Not known	Not known
SELECTIVE INHIBITORS	Imatinib (Gleevec <sup>®</sup> ), AG1295, AG1296, AGL2043, SU11248	Imatinib (Gleevec <sup>®</sup> ), AG1295, AG1296, AGL2043, SU11248, CDP860 (monoclonal antibody)
SELECTIVE ACTIVATORS	Not known	Not known
PHYSIOLOGICAL FUNCTION	Development of lungs, intestinal villi, hair follicles and glial cells during embryogenesis	Development of kidneys and blood vessels during embryogenesis; stimulation of wound healing; regulation of interstitial fluid pressure in tissues
DISEASE RELEVANCE	Glioblastoma; hypereosinophilic syndrome, gastrointestinal stroma tumor; chronic monomyelocytic leukemia (CMML)	Dermatofibrosarcoma protuberans, chronic monomyelocytic leukemia, atherosclerosis, restenosis, fibrotic conditions

### FOOTNOTES

<sup>a</sup> Can form homodimers of the respective receptor types. In addition, all PDGF isoforms, except PDGF-AA, can form PDGFR $\alpha$ /PDGFR $\beta$  heterodimers in cells expressing both receptor types.

## PDGFRs

FAMILY MEMBERS	Fms	Flt3	Kit
<b>OTHER NAMES</b>	C-fms, CD115, Colony stimulating factor 1 receptor CSF-1R, CSF1R	CD135, fetal liver kinase 2, Flk-2, Flk2, Flt-3, Flt3, Fms-like tyrosine kinase type 3, Fms-related tyrosine kinase 3, Ly72	Mast/stem cell growth factor receptor, Bs, c-KIT, c-Kit receptor tyrosine kinase CD117, Fdc, Kit, PBT, Ssm, steel factor receptor, stem cell factor receptor
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	107 kDa, 972 aa	112 kDa, 993 aa	109 kDa, 976 aa
<b>ISOFORMS</b>	Not known	Not known	Not known
<b>SPECIES</b>	Cat, human, mouse, rat	Human, mouse	Cow, dog, goat, chicken, cat, human, mouse, rat, <i>drosophila</i> , frog, zebrafish, pufferfish, horse
<b>DOMAIN ORGANIZATION</b>	Transmembrane domain 5 Ig-like domains extracellularly and a split tyrosine kinase domain intracellularly	Transmembrane domain 5 Ig-like domains extracellularly and a split tyrosine kinase domain intracellularly	Transmembrane domain 5 Ig-like domains extracellularly and a split tyrosine kinase domain intracellularly
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>708</sup>	Not known	Tyr <sup>823</sup> , Ser <sup>559</sup> , Ser <sup>721</sup> , Ser <sup>746</sup> , Ser <sup>821</sup>
<b>TISSUE DISTRIBUTION</b>	Bone marrow and in differentiated blood mononuclear cells	Bone marrow cells, dendritic cells	Fetal brain, term placenta, mast cells
<b>SUBCELLULAR LOCALIZATION</b>	Plasma membrane	Plasma membrane	Plasma membrane
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	PI3K, p85, Fmip, HSC73, PSF, Clathrin, Shp2, Sos1, Shp1, SHIP, Grb2, Cbl, NonO, SOCS1, Mg <sup>2+</sup>	Socs1, FIZ1	APS
<b>UPSTREAM ACTIVATORS</b>	CSF	FL	Stem cell factor (SCF)
<b>DOWNSTREAM ACTIVATION</b>	PI3K	STAT5a, Grb2/Sos	PI3K
<b>ACTIVATORS</b>	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Imatinib (Gleevec®)
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Differentiation of macrophages	Differentiation and mobilization of dendritic cells	Required for normal hematopoiesis, melanogenesis, and gametogenesis
<b>DISEASE RELEVANCE</b>	Chronic myelomonocytic leukemia, type M4 acute myeloblastic leukemia	Acute myelogenous leukemia, piebaldism, acute myelogenous	Gastrointestinal stromal tumor (GIST), leukemia, human mast cell disease

## FOOTNOTES