Expression and function of PDGF-C in development and stem cells

Yi Tian¹, Ying Zhan¹, Qin Jiang², Weisi Lu¹ and Xuri Li¹

¹State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangzhou 510060, People’s Republic of China
²Eye Ophthalmic Department, Affiliated Eye Hospital of Nanjing Medical University, Nanjing, People’s Republic of China

Platelet-derived growth factor C (PDGF-C) is a relatively new member of the PDGF family, discovered nearly 20 years after the finding of platelet-derived growth factor A (PDGF-A) and platelet-derived growth factor B (PDGF-B). PDGF-C is generally expressed in most organs and cell types. Studies from the past 20 years have demonstrated critical roles of PDGF-C in numerous biological, physiological and pathological processes, such as development, angiogenesis, tumour growth, tissue remodelling, wound healing, atherosclerosis, fibrosis, stem/progenitor cell regulation and metabolism. Understanding PDGF-C expression and activities thus will be of great importance to various research disciplines. In this review, however, we mainly discuss the expression and functions of PDGF-C and its receptors in development and stem cells.

1. Introduction

The platelet-derived growth factor (PDGF) family consists of four ligands (PDGF-A, -B, -C and -D) and two receptors (PDGFR-α and PDGFR-β) [1–3]. The PDGFs bind the PDGFRs and trigger their dimerization, which induces phosphorylation of the tyrosine residues in the intracellular domain of the receptors [4]. The phosphorylated receptors activate various downstream pathways, including Ras-MAPK, PI3 K and PLC-γ signalling, and participate in diverse physiological and pathological processes, such as embryonic development, angiogenesis, tumour growth, stem cell regulation and metabolism [2,5–7].

PDGF-C was discovered in 2000 [8], about 20 years after the finding of PDGF-A and PDGF-B [1,3]. PDGF-C mainly binds to PDGFR-α [8]. When PDGFR-β is co-expressed with PDGFR-α, it can be engaged by PDGF-C as well [9]. Studies from the past 20 years or so have demonstrated important roles of PDGF-C in diverse biological processes, such as development, tumour growth, angiogenesis, wound healing, tissue remodelling, fibrosis, atherosclerosis, metabolism and stem/progenitor cell regulation [5,10–16]. In this review, however, we mainly discuss the roles and expressions of PDGF-C and its receptors in human and murine development and stem cells.

2. Expression of PDGF-C and its receptors in embryonic development and adults

Embryonic development (embryogenesis), the process of embryo formation from a zygote and its further growth until birth, entails coordinated spatio-temporal regulation of gene expression, cell division and differentiation [17,18]. In mammals, such as in mice, embryogenesis is divided into pre-implantation and post-implantation stages (figure 1). In pre-implantation stage, the zygote forms a blastocyst, which is subsequently implanted in the uterus, thus entering the
In post-implantation stage [19] (figure 1). In post-implantation stage, the embryo develops into a gastrula that generates the ectoderm, mesoderm and endoderm germ layers, from which organ development (organogenesis) initiates and continues until birth [20,21] (figure 1).

Table 1. PDGF-C expression in mouse embryos.

| PDGF-C | location                                                                 | time  | references |
|--------|---------------------------------------------------------------------------|-------|------------|
| ectoderm | central nervous system, hindbrain, cerebellum, spinal cord, floorplate, ventricular and subventricular zones of cortex, epithelial tissue of choroid plexus, choroid plexus, neuron, glial cell | E9.5  | [29,30]    |
|         | neural crest cell, cartilage, osteoblast, odontoblast, inner ear, head mesenchyme of otic vesicle, frontonasal, medulla of adrenal gland | E9.5  | [31]       |
|         | skin, epidermis, follicle, root sheath, branchial arch, branchial pouch, nasal placode | E9.5  | [29]       |
|         | eye, corneal epithelium, boundary of the eyelid, retinal ganglion cell, retinal pigment epithelial cell | E16.5 | [29,30]    |
| mesoderm | somite, myotome and skeletal muscle, sphenotome, myoblast and muscles of limb bud, nuclei pulposi, epaxial muscles of trunk, myoblast and myocyte of facial and cervical muscles, notochord, myoblast of smooth and skeletal muscles, hypertrophic chondrocyte | E9.5  | [29]       |
|         | kidney, metanephric mesenchyme epithelial branche, nephric tubule and ureteric epithelium, urethra, cortex of the adrenal gland, arterial endothelial and smooth muscle cell | E12   | [29,32]    |
|         | heart, cardiomyocyte, smooth muscle cells of aorta and vena cava | E12.5 | [29,33]    |
|         | testes, coelomic epithelium, gonad-mesonephros boundary | E11.5 | [34]       |
|         | lung, epithelium, the bronchial tubule, smooth muscle, mesenchyme, trachea | E14.5 | [29]       |
|         | gut, stomach, small and large intestine, oesophagus, endodermal mucosal epithelium, mesenchyme, smooth muscle layer | E12.5 | [29]       |
|         | salivary gland, epithelial branches, mesenchyme | E12.5 | [29]       |

Post-implantation stage [19] (figure 1). In post-implantation stage, the embryo develops into a gastrula that generates the ectoderm, mesoderm and endoderm germ layers, from which organ development (organogenesis) initiates and continues until birth [20,21] (figure 1).

2.1. PDGF-C and its receptors are highly expressed in pre-implantation embryos

In the early stage of human embryonic development, such as in eight-cell stage embryos, PDGF-C and its receptors...
are abundantly expressed [22–24]. In human blastocysts, PDGF-C is detected in the inner cell mass (ICM), the pluripotent epiblast (EPI), the extra-embryonic endoderm (PrE) and trophoblast [22] with similar expression levels in PrE and EPI, and a higher level in trophoblast [23]. PDGFR-α, the major receptor used by PDGF-C, is detected as early as in four-cell stage embryos and blastocyst. PDGFR-β, which can be engaged by PDGF-C when it is co-expressed with PDGFR-α, is also detected in four-cell stage embryos [24]. In mice, like in humans, abundant Pdgf-c expression is found in early embryonic development. Pdgf-c is detected in mouse zygotes and in embryos of two-cell, eight-cell and blastocyst stages as shown by single-cell RNA sequencing [25]. Pdgf-c is upregulated in EPI at E4.5 [26,27]. Both PDGFR-α and PDGFR-β are abundantly expressed in mouse zygotes and blastocyst [25,28]. In summary, both PDGFR-α and its receptors are abundantly expressed in human and mouse pre-implantation embryos, suggesting the possible effects of PDGF-C on early embryogenesis.

### 2.2. PDGF-C and its receptors are expressed in all the three germ layers in post-implantation embryos

In post-implantation embryos, PDGF-C is highly expressed in all the three germ layers and their derivatives (table 1). In the ectoderm, PDGF-C is expressed in the neural tube and its derivatives, such as in the cerebral cortex, floorplate, spinal cord, cerebellum and hindbrain of the central nervous system (CNS) [29,35,36] (table 1). Expression of PDGF-C is also found in the cephalic neural crest and its derivatives, such as in the eye, follicles, branchial arches and pouches in the mesenchyme tissues [45], somite and its derivatives [45,46], bladder, kidney [8,47], heart [38,45] and testes [48]. Moreover, PDGFR-α is expressed in the endoderm lineage, such as the lung [49–51] and salivary gland [52,53]. In the ectoderm lineage, PDGFR-β is found in the CNS [53–55] and eye [37]. In the mesoderm lineage, PDGFR-β is detected in the kidney [43], heart [56] and testes [48]. PDGFR-β is also expressed in the endoderm lineage, such as the lung [57–59] (table 2). Thus, the general expression of PDGF-C and its derivatives is widespread throughout the embryo, indicating its crucial role in various developmental processes.
receptors in the three germ layers in post-implantation embryos suggest possible functions of PDGF-C during organogenesis.

2.3. Expression of PDGF-C and its receptors in adults

In humans, PDGF-C is generally expressed in most adult organs and tissues, such as in the vasculature, heart, brain, kidney, liver, testes, lung, pancreas, ovary, placenta, skeletal muscle, thymus, prostate gland, adrenal gland, breast, colon, uterus and small intestine [60–64] (table 3). Human PDGFR-α and PDGFR-β are also expressed in most of these organs, such as in the brain, kidney, testes, lung and eye [48,83,84].

In mice, PDGF-C is also widely expressed in various organs and cell types, including the brain, heart, vasculature [29,36], kidney, liver, testes and lung [80] (table 3). In the vascular system, PDGF-C is abundantly expressed in vascular endothelial cells (ECs) [60,65], vascular smooth muscle cells (SMCs) [66] and pericytes (PCs) [85]. PDGF-C is also expressed in mouse monocytes, macrophages, platelets and fibroblasts [67]. In the heart, PDGF-C is detected in mouse cardiac fibroblasts and myofibres [8,33]. In the neural system, PDGF-C is highly expressed in projection neurons, interneurons in the cerebral cortex, choroid plexus, spinal cord neurons [36], cerebellum [70], anterior olfactory nucleus, pontine nuclei [36] and neuronal cells in the cochlea [30]. PDGF-C is also detected in mouse glial cells, such as astrocytes [86], microglia [71] and oligodendrocytes [72]. Other mouse organs expressing PDGF-C include the adrenal gland, colon, duodenum, ovary, placenta, thymus and small intestine [82] (table 3). Mouse PDGFR-α and PDGFR-β are expressed in most organs as well, such as in the heart, brain, lung, kidney, spleen, mammary gland, ovary and testes [87,88] (table 4).

3. Regulation of PDGF-C expression

PDGF-C activity must be tightly controlled, and uncontrolled PDGF-C expression has been reported to be associated with numerous pathological conditions, such as choroidal neovascularization [95], chronic myocarditis [96], glomerulosclerosis [64], tissue fibrosis [12,15,97–99], atherosclerosis [100] and various tumours [11,98,101–106].

Several transcription factors are reported to promote PDGF-C expression, including early growth reactive protein 1 (EGR1), STAT6 [81], HuR (human embryonic lethial abnormal vision-like protein) [107] and EWS/FLI [106]. In lung fibroblasts, PDGF-C is upregulated by IL-13 via STAT6 and EGR-1 [81]. In SMCs, PDGF-C is upregulated by EGR-1 through ATII-AT1R or Erk [66,108]. In breast cancer, PDGF-C expression is increased by HuR after its binding by EGR-1 through ATII-AT1R or Erk [66,108]. In breast cancer, PDGF-C expression is increased by HuR after its bind-

4. PDGF-C is critical for the development of multiple organs and tissues

It has been shown that PDGF-C has a vital role in embryonic development. Genetic deletion of Pdgf-c leads to embryonic lethality in mice on a 129/S background [116]. PDGF-C deficiency results in multiple defects in various organs and

| Table 4. Expression of PDGFR-α and PDGFR-β in adults. |
|----------------|------------------|
| PDGFR-α        | PDGFR-β          |
| vascular system| vascular system   |
| ECs, SMCs, PCs, epicardium, myocardium, endocardium, fibroblasts |
| neural system  | hippocampus, brainstem, spinal cord, neurons, astrocytes, Schwann cells |
| kidney         | mesangial cells, SMCs, glomeruli, tubules testes |
| lung           | Leydig cells     |
| lung           | Leydig cells     |
| lung           | RPE cells, retina, corneal epithelium, RGCs |
| PDGFR-β        | vascular system   |
| ECs, SMCs, PCs, myocardium, fibroblasts |
| neural system  | hippocampal, cortical neurons, Schwann cells |
| kidney         | mesangial cells, parietal epithelial cells, interstitial fibroblasts |
| testes         | Leydig cells     |
| RPE cells      | Leydig cells     |
| RPE cells      | Leydig cells     |
| RPE cells, retina, corneal fibroblasts, RGCs |

embryos, retinoic acid administration markedly downregulated PDGF-C and PDGFR-α expression, leading to branchial arch malformation and impaired proliferation of mouse embryonic palatal mesenchymal cells (MEPMC) [113,114]. In human retinal pigment epithelial cells, interleukin 1 beta (IL-1β) downregulates PDGF-C and inhibits RPE proliferation and migration [115]. In human hepatic stellate cells, microRNA-29a downregulates PDGF-C to suppress cell migration and proliferation [77]. Thus, modulating these factors may be of usage to regulate PDGF-C expression levels.
tissues, such as in the vascular and neural systems, lung, palate and kidney [6, 14, 117] (table 5).

4.1. Vascular development

PDGF-C is essential for the proper development of the vascular network (table 5). Genetic deletion of \( Pdgf-c \) in both 129/S and C57BL/6 mice caused vascular defects, such as extracranial vessel haemorrhage [116], and abnormal morphology, density and poor SMC coverage of cerebral blood vessels [138]. Genetic deletion of the major receptor for PDGF-C, \( Pdgfr-\alpha \), also results in various vascular defects, such as abnormal yolk sac vasculature and extensive bleeding in various organs [139]. Moreover, \( Pdgfr-\alpha \) mutation in mice impairs the proper development of aortic and the pulmonary vessels [44] (table 5). These data thus demonstrate an essential role of PDGF-C and its receptor during the development of the vascular system.

4.2. Neural system

The neural tube is the primitive central structure of the nervous system during embryonic development, from which the brain and spinal cord develop [140]. PDGF-C is required for the development of the neural tube, notochord and the mesenchymal tissues surrounding them [116, 138]. Genetic deletion of the major receptor for PDGF-C, \( Pdgf-\alpha \), also results in various vascular defects, such as abnormal yolk sac vasculature and extensive bleeding in various organs [139]. Moreover, \( Pdgf-\alpha \) mutation in mice impairs the proper development of aortic and the pulmonary vessels [44] (table 5). These data thus demonstrate an essential role of PDGF-C and its receptor during the development of the vascular system.

4.3. Lung

PDGF-C plays a critical role in lung development (table 5). PDGF-C overexpression resulted in various defects in the lung and embryonic lethality, including the excessive proliferation of mesenchymal cells, mesenchymal–epithelial disruption and enlarged and immature lungs [144]. Consistently, genetic deletion of \( Pdgf-c \) in mice caused emphysema [120]. In addition, PDGF-C has been shown to promote proliferation and inhibits apoptosis and differentiation of lung mesenchymal cells [80]. Moreover, PDGF-C prevents the differentiation of distal airway and airspace epithelial cells into type I alveolar epithelial cells, which constitute the structure of the alveoli and mediate gas exchange [145]. Of the two receptors for PDGF-C, PDGFR-\( \beta \) seems to be more important for lung development since PDGFR-\( \beta \) activity is critically required for embryonic lung growth [57], and inhibition of PDGFR-\( \beta \) signalling with antisense oligodeoxynucleotides significantly reduced embryonic lung epithelial growth and lung size [57, 146]. In addition, PDGF-\( \alpha \) signalling has been shown to be vital for lung alveolarization [147]. Thus, both PDGF-C and PDGFR\( s \) are critical for lung development.

4.4. Palate and kidney

The mouse palate forms at E11.5 from the maxillary processes and mainly comprises epithelial and mesenchymal cells [113, 116]. Genetic deletion of \( Pdgf-c \) or blocking PDGF-C with neutralization antibody leads to palate branchial arch abnormalities, complete cleft palate and embryonic lethality [113, 116] (table 5). Consistently, genetic deletion of the major
Table 5. Phenotypes of Pdgf-c and Pdgfr deficient mice.

| Phenotype                                                                 | References |
|---------------------------------------------------------------------------|------------|
| Pdgf-c<sup>−/−</sup>                                                       |            |
| perinatal lethality, complete cleft of the secondary palate, abnormal branchial arches | [116]      |
| reduced choroidal neovascularization and ischaemia-induced retinal neovascularization, reduced retinal ganglion cell survival after optic nerve crush injury | [30,95]    |
| abnormal cerebral vascularization, asymmetry of the cerebral lateral ventricles, abnormal ventricular lining | [138]      |
| reduction of renal fibrosis and leucocyte infiltration in response to unilateral ureteral obstruction, mitigated glomerular injury and hypertension | [12,118]  |
| lung emphysema, reduction of revascularization in ischaemia limbs of diabetes | [118]      |
| 
| Pdgfr-α<sup>−/−</sup>                                                      |            |
| perinatal lethality, complete cleft palate, connective tissue deficiency | [119]      |
| neural crest origin defects and incomplete cephalic closure, craniofacial abnormality, abnormal meninges, neuronal over-migration in the cerebral cortex, spina bifida | [120]      |
| abnormal cardiac and cephalic neural crest cell development, reduction of cardiac fibroblasts, cardiovascular defects, heart deformity | [121,122] |
| reduction of hepatic stellate cell activation and liver fibrosis          | [123]      |
| lung emphysema, lung hypoplasia, reduction of SMPCs in the lungs           | [49]       |
| abnormal gastrointestinal mucosal lining, skeletal defect                  | [124]      |
| 
| Pdgfr-β<sup>−/−</sup>                                                      |            |
| perinatal lethality, reduction of neurons in the superior colliculus and hippocampus, abnormal hippocampal spine, brain oedema, exacerbated cerebral damage after cryogenic injury, BBB integrity breakdown after cerebral ischaemia, demyelination | [125–130] |
| loss of VSMCs and PCs, dilated heart and aorta, anaemia, thrombocytopenia, microvessel leakage, microaneurysm formation, haemorrhage | [131]      |
| absence of mesangial cells of glomeruli, dilated capillaries, reduction of mesangial cells | [132]      |
| reduced proliferation and migration of skin fibroblasts, skin wound healing defect, reduced adipose tissue neovascularization and chronic inflammation, defective periosteal bone formation and regeneration | [133–135] |
| enlarged hepatic injury and infarct volume after ischaemic stroke          | [136,137]  |

receptor for PDGF-C, Pdgfr-α, also results in cleft palate [116]. By contrast, loss of Pdgfr-β does not cause cleft palate, suggesting a unique role of the PDGF-C–PDGFR-α axis in palate development. In addition, PDGF-C plays important roles in kidney development by promoting the formation of ureteric buds and mesangial cells in the glomerulus as well as the maturation of kidney arteries and arterioles [8,64]. PDGFR-α is highly expressed in kidney interstitial cells and arterial and venous vessels, suggesting a role of PDGFR-α in kidney development [148]. Genetic deletion of Pdgfr-β leads to glomerular mesangial cell failure in mice, demonstrating critical roles of PDGFR-β in glomerular morphogenesis [148].

5. PDGF-C and its receptors are expressed in various types of stem cells

Stem cells generally include embryonic stem cells (ESCs), adult stem cells (ASCs) and induced pluripotent stem cells (iPSCs). ESCs are isolated from the ICM of E3.5 embryos [149]. These pluripotent stem cells form derivatives of all the three germ layers except the trophoderm [149]. ASCs are multipotent stem cells found in adult tissues and can differentiate into various cell types [150]. iPSCs are adult somatic cells reprogrammed by overexpressing the key transcription factors octamer-binding transcription factor 4 (OCT4), sex-determining region Y-box 2 (SOX2), MYC proto-oncogene (c-MYC) and Kruppel-like factor 4 (KLF4) with differentiation capacities similar to ESCs [151–153]. PDGF-C, PDGFR-α and PDGFR-β are expressed in both mouse and human ESCs [23,25,154–156]. PDGF-C expression is also found in various ASCs, such as human mesenchymal stem cells (MSCs) [68], adipose-derived stem cells [157] and vascular stem/progenitor cells [158,159]. Both PDGFR-α and PDGFR-β are expressed in human MSCs [160], adipose-derived stem cells [161–163], vascular stem/progenitor cells [164] and neural stem cells (NSCs) [165–167]. PDGFR-β is also expressed in human haematopoietic stem cells (HSCs) [168] and mouse spermatogonial stem cells [169]. In mouse iPSCs, PDGF-C is also expressed as revealed by microarray analysis [170]. PDGFR-β, but not PDGFR-α, is detected in both human and mouse iPSCs [171,172]. Thus, the expression of PDGF-C and its receptors in various types of stem cells suggests potential effects of them in stem cell regulation.

6. Effects of PDGF-C and PDGFRs on stem cells

6.1. Adult stem cell (ASC)

PDGF-C and the PDGFRs have been demonstrated to have important effects on various types of ASCs (table 6). It has
been shown that PDGF-C promotes human MSC proliferation and maintains their multipotency by activating PDGFR-α signalling [68] (table 6). Also, in mouse MSCs, PDGF-C promotes MSC migration via PDGFR-α- and PDGFR-β-induced PI3 K signalling [185]. In addition, it is reported that PDGF-C regulates mouse adipose-derived stem cells and subsequently promotes hair growth [157]. Consistently, PDGFR-α has been shown to promote the proliferation of mouse dermal CD24+ adipose-derived stem cells and therefore maintains the adipocyte precursor cell population [163]. Moreover, PDGFR-β is reported to promote the proliferation of human adipose-derived stem cells [161]. Furthermore, PDGF-C also plays important roles in the regulation of vascular stem/progenitor cells. PDGF-C overexpression increased endothelial progenitor cell (EPC) proliferation, migration and adhesion [158]. PDGF-C also induced EPCs to differentiate into ECs and SMCs, thereby promoting the revascularization of ischaemic tissues [69,186]. In addition, it has been shown that PDGF-C activates PDGFR-α in human bone marrow-derived AC133+CD34+ cells and induce their differentiate into ECs and SMCs [95].

These observations thus suggest possible effects of PDGF-C on ESCs and warrant further studies to look into it.

### 6.2. Embryonic stem cell (ESC)

PDGF-C is highly expressed in the very early stage of embryonic development [22–24], and genetic deletion of Pdgf-c leads to embryonic lethality [116]. Moreover, both receptors for PDGF-C, PDGFR-α and PDGFR-β, are highly expressed in ESCs [23,25,154–156], further suggesting potential effects of PDGF-C on ESCs. It has been shown that PDGFRs are critical for the undifferentiated state of human ESCs, since inhibition of the PDGFRs downregulated the master pluripotency factors NANOG and OCT4 and led to ESC differentiation [173] (table 6), suggesting a potential role of PDGF-C in maintaining ESC pluripotency. Moreover, it is reported that PDGFR-α induces ERK activation inhibits ESC apoptosis [187].

On the other hand, other studies reported that the PDGFR signalling induces differentiation of ESCs into various cell types. For example, inhibition of PDGFR-α by microRNA-218 (miR-218) suppressed ESC migration and differentiation [188], while upregulation of PDGFR-α by mix-like protein 1 (Mixl1) induced ESC differentiation into mesendoderm cells [189]. Moreover, it has been shown that PDGFR-α induces ESC differentiation into blood cells [190], and PDGR-β activation by cyclic strain induces ESC differentiation into vascular SMCs [191]. Furthermore, PDGFR-β is reported to activate the STAT5 and phosphatidylinositol-3 kinase (PI3 K) pathways and induce ESC differentiation into bone marrow cells [192].

### 7. Concluding remarks

Since the discovery of PDGF-C about two decades ago, studies have demonstrated its critical roles in embryonic development. Loss or overexpression of PDGF-C lead to various developmental defects in multiple organs and tissues, such as in the neural system, palate, lung, kidney and the vasculature. In addition, PDGF-C and its receptors are abundantly expressed in various types of stem cells, such as ESCs, ASCs and iPSCs. PDGFRs have been amply demonstrated to regulate stem cell pluripotency or differentiation, thus suggesting a possible role of PDGF-C in these processes. Future studies are warranted to verify whether and how PDGF-C plays a role in stem cell regulation, particularly, in neural, lung, palate or kidney progenitor/stem cells. It is also critical to identify the regulatory factors governing PDGF-C expression, the discovery of which might lead to new possibilities of therapeutic interventions for developmental defects or stem cell therapy.

Data accessibility. This article has no additional data.
Authors’ contributions. X.L. and W.L. conceived the conceptual basis for the review, and revised the review, and designed the figures and tables together. Q.J. contributed to the writing of the manuscript. Y.T. and Y.Z. wrote the manuscript and generated the figures and tables together.

Competing interests. We declare we have no competing interests.

Funding. This study is supported by the National Natural Science Foundation of China (grant nos. 82170983 and 81870679 to Q.J.), Program of Guangzhou Scientific Research Plan (grant nos. 202102010179), Natural Science Foundation of Guangdong Province (grant nos. 2019A1515010229 and 2021A1515010848), the Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science (grant no. 2020B121206033), Guangzhou basic and applied research program (grant no. 20212020146) and the Fundamental Research Funds for the Central Universities (grant no. 19ykpy151).

Acknowledgements. This study is supported by the State Key Laboratory of Ophthalmology (SKLO), Zhongshan Ophthalmic Center (ZOC) at the Sun Yat-Sen University (SYSU).

References

1. Lu W, Li X. 2018 PDGFs and their receptors in vascular stem/progenitor cells: functions and therapeutic potential in retinal vasculopathy. Mol. Aspects Med. 62, 22–32. (doi:10.1016/j.mam.2017.10.001)

2. Andrei A, Galliani R, Bethelchz C. 2008 Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 22, 1276–1312. (doi:10.1101/gad.1653708)

3. Lee C, Zhang F, Tang Z, Liu Y, Li X. 2015 PDGF-C: a new performer in the neurovascular interplay. Trends Mol. Med. 19, 474–486. (doi:10.1016/j.tmm.2013.04.006)

4. Kelly JD, Haldeman BA, Murray MJ, Seifert RA, Bowen-Pope DF, Cooper JA, Kaalezmas A. 1991 Platelet-derived growth factor (PDGF) stimulates PDGF receptor subunit dimerization and intersubunit trans-phosphorylation. J. Biol. Chem. 266, 8987–8992. (doi:10.1002/jbc.26605288)

5. Cox N et al. 2021 Diet-regulated production of PDGFcc by macrophages controls energy storage. Science (New York, NY) 373, eabe9383. (doi:10.1126/science.abe9383)

6. Lee C, Li X. 2018 Platelet-derived growth factor-C and -D in the cardiovascular system and diseases. Mol. Aspects Med. 62, 12–21. (doi:10.1016/j.mam.2017.09.005)

7. Sun Y, Liu WZ, Liu T, Feng X, Yang N, Zhou HF. 2015 Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. J. Recept. Signal Transduct. Res. 35, 600–604. (doi:10.1080/1070932X.2015.1030412)

8. Li X et al. 2000 PDGF-C is a new protease-activated ligand for the PDGF alpha-receptor. Nat. Cell. Biol. 2, 302–309. (doi:10.1038/sj.ncb.4200209)

9. Cao R, Bräkenhielm E, Li X, Pietras K, Widenfalk J, Ostman A, Eriksson U, Cao Y. 2002 Angiogenesis stimulated by PDGF-CC, a novel member in the PDGF family, involves activation of PDGFR-αα and -cαβ receptors. FASEB J. 16, 1575–1583. (doi:10.1096/fj.02-0319com)

10. Gazuz-Bilska AT, Johnson ML, Bilski JJ, Redmar DA, Reynolds LP, Abdullah A, Abdullah KM. 2003 Wound healing: the role of growth factors. Drugs Today (Barcelona, Spain: 1998) 39, 787–800. (doi:10.1385/DT:2003:39:7.799472)

11. Zwemer JP, May WA. 2002 Dominant negative PDGF-C inhibits growth of Ewing family tumor cell lines. Oncogene 21, 3847–3854. (doi:10.1038/sj.onc.1205486)

12. van Roeyen CRC et al. 2019 Identification of platelet-derived growth factor C as a mediator of both renal fibrosis and hypertension. Kidney Int. 95, 1103–1119. (doi:10.1016/j.kint.2018.11.031)

13. Pettullo M, Scambia G, Ferrandina G. 2012 Novel targets for VEGF-independent anti-angiogenic drugs. Expert Opin Investig. Drugs 21, 451–472. (doi:10.1517/13543748.2012.661715)

14. Folestad E, Kunath A, Wågsäter D. 2018 PDGF-C and -D signaling in vascular diseases and animal models. Mol. Aspects Med. 62, 1–11. (doi:10.1016/j.mam.2018.01.005)

15. Klinkhammer BM, Floege J, Boor P. 2018 PDGF in organ fibrosis. Mol. Aspects Med. 62, 44–62. (doi:10.1016/j.mam.2017.11.008)

16. Reigstad LJ, Varhaug JE, Lillehaug JR. 2005 Structural and functional specificities of PDGF-C and PDGF-D, the novel members of the platelet-derived growth factors family. FEBS J. 272, 5723–5741. (doi:10.1111/j.1742-4658.2005.04989.x)

17. 2017 Shaping embryonic development. Nat. Chem. Biol. 13, 559. (doi:10.1038/nchembio.2403)

18. 2017 Asparagine synthetase: function, structure, and role in disease. J. Biol. Chem. 292, 19 952–19 958. (doi:10.1074/jbc.R117.819060)

19. Maitre JL. 2017 Mechanics of blastocyst morphogenesis. Biol. Cell 109, 323–338. (doi:10.1111/boc.201700029)

20. McDole K, Guignard L, Amat F, Berger A, Malandain S, 2017 Single-cell RNA-Seq profiling of separate, but adjacent cell layers of the mouse embryo. Development 145, 1045–1058. (doi:10.1242/dev.1145.10.045)

21. Aase K, Abramsson A, Karlsson L, Bethelchz C, Eriksson U. 2002 Expression analysis of PDGF-C and -D in adult and developing mouse tissues. Mech. Dev. 110, 187–191. (doi:10.1016/s0925-4773(01)00560-3)

22. Tang Z et al. 2010 Survival effect of PDGF-CC rescues neurons from apoptosis in both brain and retina by regulating GSK3β phosphorylation. J. Exp. Med. 207, 867–880. (doi:10.1084/jem.20091704)

23. Lee YW, Ozeki M, Juhu SK, Lin J. 2004 Expression of platelet-derived growth factor in the developing cochlea of rats. Acta Otolaryngol. 124, 558–562. (doi:10.1080/00016480410016577)

24. Eftner F, Ostendorf T, Van Roeyen C, Kitahara M, Li X, Aase K, Gröne HJ, Eriksson U, Fleckner J. 2002 Expression of a novel PDGF isoform, PDGF-C, in normal and diseased rat kidney. J. Am. Soc. Nephrol. 13, 910–917. (doi:10.1681/asn.20011391)

25. Pontén A, Li X, Thörén P, Aase K, Sjöblom T, Ostman A, Eriksson U. 2003 Transgenic overexpression of platelet-derived growth factor-C in the mouse heart induces cardiac fibrosis, hypertrophy, and dilated cardiomyopathy. Am. J. Pathol. 163, 673–682. (doi:10.1016/s0002-9440(10)63594-2)
34. Brennan J, Tillmann C, Capel B. 2003 Pdgfr-cc mediates testis cord organization and fetal Leydig cell development in the XY gonad. Gene Dev. 17, 800–810. (doi:10.1101/gad.1052503)

35. Ding H, Wu X, Kim I, Tam PP, Koh GY, Nagy A. 2000 The mouse Pdgf gene: dynamic expression in embryonic tissues during organogenesis. Mech. Dev. 96, 209–213. (doi:10.1016/s0925-4773(00)00425-1)

36. Hamada T, Utei K, Imaji K, Takahashi F, Onodera M, H, Mishima T, Miyata Y. 2002 The expression of SCDFG/PDGF-C/fallotin and SCDFG-B/PDGF-D in the rat central nervous system. Mech. Dev. 112, 161–164. (doi:10.1016/s0925-4773(01)00625-6)

37. Mudhar HS, Pollock RA, Wang C, Stiles CD, et al. 2002 Expression of PDGF-A and PDGF-B signaling is required for lung growth and the formation of alveoli but not for early lung branching morphogenesis. Dev. Dyn. 223, 155–162. (doi:10.1002/dvdy.1225)

38. Bostrom H et al. 1996 PDGF-A signaling is a critical event in lung alveolar myofibroblast development and alveogenesis. Cell 85, 863–873. (doi:10.1016/s0092-8674(00)81270-2)

39. Lindahl P, Karlsson L, Hellström M, Gebre-Medhin S, et al. 2010 Enlarged lateral vertebral column and improper vertebral fusion in Patch mice. J. Biol. Chem. 285, 24242–24250. (doi:10.1074/jbc.M110017200)

40. Akker Vd et al. 2008 PDGF-B signaling is important for murine cardiac development: its role in developing atrioventricular valves, coronaries, and cardiac innervation. Dev. Dyn. 237, 494–503. (doi:10.1002/dvdy.21469)

41. Hall A, Giese NA, Richardson WD. 1996 Spinal cord oligodendrocytes develop from ventrally derived progenitor cells that express PDGF alpha-receptors. Development 122, 4085–4094. (doi:10.1242/dev.122.12.4085)

42. Fruttiger M et al. 1999 Defective oligodendrocyte development and severe hypomyelination in PDGF-A knockout mice. Development 126, 457–467. (doi:10.1242/dev.126.3.457)

43. Soriano P. 1994 Abnormal kidney development and hematological disorders in Pdgf beta-receptor mutant mice. Genes Dev. 8, 1888–1896. (doi:10.1101/gad.8.16.1888)

44. Morrison-Graham K, Schatteman GC, Bork T, Bowen-Pope DF, Weston JA. 1992 A PDGF receptor mutation in the mouse (Patch) perturbs the development of a non-neural subset of neural crest-derived cells. Development 115, 133–142. (doi:10.1242/dev.115.1.133)

45. Schatteman GC, Morrison-Graham K, van Koppens A, Weston JA, Bowen-Pope DF. 1992 Regulation and role of PDGF receptor alpha-subunit expression during embryogenesis. Development 115, 123–131. (doi:10.1242/dev.115.1.123)

46. Tallquist MD, Weismann KE, Hellström M, Soriano P. 2000 Early myotome specification regulates PDGFα expression and axial skeleton development. Development 127, 5059–5070. (doi:10.1242/dev.127.23.5059)

47. On-Urrtager A, Bedford MT, Do MS, Eisenbach L, Lonai P. 1992 Developmental expression of the alpha receptor for platelet-derived growth factor, which is deleted in the embryonic lethal Patch mutation. Development 115, 289–303. (doi:10.1242/dev.115.1.289)

48. Basciani S et al. 2002 Expression of platelet-derived growth factor-A (PDGF-A), PDGF-B, and PDGF receptor-alpha and -beta during human testicular development and disease. J. Clin. Endocrinol. Metab. 87, 2310–2319. (doi:10.1210/jem.87.5.8476)

49. Dong H, Wu X, Kim I, Tam PP, Koh GY, Nagy A. 2002 The mouse Pdgf gene: dynamic expression in embryonic tissues during organogenesis. Mech. Dev. 96, 209–213. (doi:10.1016/s0925-4773(00)00425-1)

50. Boström H et al. 1996 PDGF-A signaling is a critical event in lung alveolar myofibroblast development and alveogenesis. Cell 85, 863–873. (doi:10.1016/s0092-8674(00)81270-2)

51. Lindahl P, Karlsson L, Hellström M, Gebre-Medhin S, et al. 2010 Enlarged lateral vertebral column and improper vertebral fusion in Patch mice. J. Biol. Chem. 285, 24242–24250. (doi:10.1074/jbc.M110017200)

52. Fang L et al. 2004 PDGF-C is a selective alpha platelet-derived growth factor receptor agonist that is highly expressed in platelet alpha granules and vascular smooth muscle. Arterioscler. Thromb. Vasc. Biol. 24, 787–792. (doi:10.1161/01.atv.0000120785.82268.bb)

53. Eitner F, Ostendorf T, Kretzler M, Cohen GD, Eriksson U, Gröne HJ, Floege J. 2003 PDGF-C expression in the developing and normal adult human kidney and in glomerular diseases. J. Am. Soc. Nephrol. 14, 1145–1153. (doi:10.1093/asn.asn.2002.14.5.1145)

54. Gilbertson DG et al. 2001 Platelet-derived growth factor C (PDGF-C), a novel growth factor that binds to PDGF alpha and beta receptor. J. Biol. Chem. 276, 4028–4035. (doi:10.1074/jbc.M010652000)

55. Midgie VC, Khachigian LM. 2004 Fibroblast growth factor-2 induction of platelet-derived growth factor-C chain transcription in vascular smooth muscle cells is ERK-dependent but not JNK-dependent and mediated by Eg-1. J. Biol. Chem. 279, 27999–28005. (doi:10.1074/jbc.M010652000)

56. Wågsäter D, Zhu C, Björck HM, Eriksson P. 2009 Effects of PDGF-C and PDGF-D on monocyte migration and MMP-2 and MMP-9 expression. Atherosclerosis 202, 415–423. (doi:10.1016/j.atherosclerosis.2008.04.050)

57. Wågsäter D, Zhu C, Björck HM, Eriksson P. 2009 Effects of PDGF-C and PDGF-D on monocyte migration and MMP-2 and MMP-9 expression. Atherosclerosis 202, 415–423. (doi:10.1016/j.atherosclerosis.2008.04.050)

58. Sotoca AM, Roelofs-Hendriks J, Boeren S, van der Kraan PM, Vervoort J, van Zoelen EJ, Piek E. 2013 Comparative proteome approach demonstrates that platelet-derived growth factor C and D efficiently induce proliferation while maintaining multipotency of hMSCs. Exp. Cell Res. 319, 2649–2662. (doi:10.1016/j.yexcr.2013.07.027)

59. Li X et al. 2005 Revascularization of ischemic tissues by PDGF-CC via effects on endothelial cells and their progenitors. J. Clin. Invest. 115, 118–127. (doi:10.1172/JCI19189)

60. Wu X, Liu W, Ding H. 2018 A Pdgf-c(CreERT2) knock-in mouse model for tracing PDGF-C cell
lineages during development. Genesis 56, e23092. (doi:10.1002/dvg.23092)

71. Su Ef et al. 2017 Microglial-mediated PDGF-CC activation increases cerebrovascular permeability during ischemic stroke. Acta Neuropathol. 134, 585–604. (doi:10.1007/s00401-017-1749-z)

72. Murtie JC, Zhou XY, Le TQ, Vana AC, Armstrong RC. 2005 PDGF and FGF2 pathways regulate distinct oligodendrocyte lineage responses in experimental demyelination with spontaneous remyelination. Neurobiol. Dis. 19, 171–182. (doi:10.1016/j.nbd.2004.12.006)

73. Huang Y et al. 2014 Oligodendrocyte progenitor cells promote neovascularization in glioma by disrupting the blood-brain barrier. Cancer Res. 74, 1011–1021. (doi:10.1158/0008-5472.Can-13-1072)

74. Bakir B, Sari EK, Aydin BD, Yildiz SE. 2015 Characterization of human PDGF-B-positive pericytes from IFP and non-IFP lungs. Am. J. Physiol. Lung Cell. Mol. Physiol. 315, L991–L1002. (doi:10.1152/ajplung.00289.2018)

75. Li X, Kumar A, Zhang F, Lee C, Li Y, Tang Z, Arjuna P. 2010 VEGF-independent angiogenic pathways induced by PDGF-C. Onco Targets 1, 309–314. (doi:10.18632/oncotarget.141)

76. Wang Y, Abu-Asab MS, Yu CR, Tang Z, Shen D, Tuo J, Li X, Chan CC. 2014 Platelet-derived growth factor (PDGF)-C inhibits neurtroperal apoptosis in a murine model of focal retinal degeneration. Lab. Invest. 94, 674–682. (doi:10.1038/labinvest.2014.60)

77. Matsuromoto Y, Ifami S, Kureda M, Yoshizato K, Kawada N, Murakami Y. 2016 MiR-29a assists in disrupting the blood-brain barrier. Dev. Brain Res. 262, (doi:10.1038/nature14475)

78. Mooring M et al. 2020 Hepatocyte stress increases expression of yes-associated protein and transcriptional coactivator with PDZ-binding motif in hepatocytes to promote parenchymal inflammation and fibrosis. Hepatology 71, 1831–1830. (doi:10.1002/hep.3092)

79. Lee JI et al. 2016 Role of Smad3 in platelet-derived growth factor-C-induced liver fibrosis. Am. J. Physiol. Cell Physiol. 310, C436–C445. (doi:10.1152/ajpcell.00423.2014)

80. Gouveia L, Betsholtz C, Andrae J. 2017 Expression analysis of platelet-derived growth factor receptor alpha and its ligands in the developing mouse lung. Physiol. Rep. 5, e13092. (doi:10.14834/pdy.13092)

81. Ingram JL, Antao-Menezes A, Mangum JB, Lyght O, Lee PJ, Elias JA, Bonner KC. 2006 Opposing actions of Stat1 and Stat6 on IL-13-induced up-regulation of early growth response-1 and platelet-derived growth factor ligands in pulmonary fibroblasts. J. Immunol. 177, 4141–4148. (doi:10.4049/jimmunol.177.6.4141)

82. Yue F et al. 2014 A comparative encyclopedia of DNA elements in the mouse genome. Nature 515, 355–364. (doi:10.1038/nature13992)

83. Uehara G, Suzuki D, Toyoda M, Umezono T, Sakai H. 2004 Glomerular expression of platelet-derived growth factor (PDGF)-A, -B chain and PDGF receptor-alpha, -beta in human diabetic nephropathy. Clin. Exp. Nephrol. 8, 36–42. (doi:10.1007/s10157-003-0265-8)

84. Wilson CL, Stephenson SE, Higuero JP, Feghali-Bostwick C, Hung CF, Schnapp LM. 2018 Characterization of human PDGF-B-positive pericytes from IFP and non-IFP lungs. Am. J. Physiol. Lung Cell. Mol. Physiol. 315, L991–L1002. (doi:10.1152/ajplung.00289.2018)

85. Kuzmanov A, Wiesbeck B, Rezaei M, Ketteler H, Breier G. 2012 Overexpression of factor inhibiting HIF-1 enhances vessel maturation and tumor growth via platelet-derived growth factor-C. Int. J. Cancer 133, E603–E613. (doi:10.1002/ijc.27360)

86. Miyata T, Toho T, Nonoguchi N, Furuse M, Kawabara H, Yoritsune E, Kawabata S, Kuroiwa T, Miyatake S. 2014 The roles of platelet-derived growth factors and their receptors in brain radiation necrosis. Radiat. Oncol. 9, 51. (doi:10.1186/1748-717X-9-51)

87. Armulik A, Genové G, Betsholtz C. 2011 Pericytes: developing and mature human kidneys. Kidney Int. 79, 1–18. (doi:10.1038/ki.2010.57)

88. Duff MO, Olson S, Wei X, Garrett SC, Osman A, Drachenberg CB, Coleman RA, Wade JB. 2018 Oligodendrocyte progenitor cells promote neovascularization in glioma by suppressing PDGFR-α and PDGFR-β in atherosclerotic human arteries. Eur. J. Clin. Invest. 49, 320–327. (doi:10.1111/ecv.12282)

89. Weinman EJ, Lakkis J, Al-Bloj M, Lasky JA. 2004 Modulation of PDGF-C and PDGF-D expression during bleomycin-induced lung fibrosis. Am. J. Physiol. Lung Cell. Mol. Physiol. 286, L182–L188.

90. Weinman EJ, Lakkis J, Al-Bloj M, Lasky JA. 2004 Modulation of PDGF-C and PDGF-D ligands may play a role in the development of brain tumors. Cancer Res. 62, 3729–3735.

91. Donnem T, Al-Saad S, Andersson S, Busund L, Bremnes RM. 2008 Prognostic impact of platelet-derived growth factors (PDGF) and their receptors on outcome in colorectal cancer. Cancer Res. 68, 4634–4641. (doi:10.1158/0008-5472.Can-08-0791)

92. Buben AM et al. 2011 Impact of exploratory biomarkers on the treatment effect of bevacizumab in metastatic breast cancer. Clin. Cancer Res. 17, 372–381. (doi:10.1158/1078-0432.CCR-10-1791)

93. Manzat Saplacan RM, Balacescu L, Gherman C, Chira C, Crişan M. 2012 Platelet-derived growth factors (PDGF)-C and -D and their receptors PDGFR-α and PDGFR-β in athrosclerotic human arteries. Cardiovasc. J. 39, 320–327. (doi:10.1111/j.1747-1440.2010.00584.x)

94. Zhou L, Zhang J, Laboy M, Lasky JA. 2004 Modulation of PDGF-C and PDGF-D expression during bleomycin-induced lung fibrosis. J. Am. Soc. Nephrol. 15, 273–280. (doi:10.1158/1078-2247onal.1204133)

95. Zhuo Y, Zhang J, Laboy M, Lasky JA. 2004 Modulation of PDGF-C and PDGF-D expression during bleomycin-induced lung fibrosis. J. Am. Soc. Nephrol. 15, 273–280. (doi:10.1158/1078-2247onal.1204133)
114. Han J, Xiao Y, Lin J, Li Y. 2006 PDGF-C controls

117. Betsholtz C. 2004 Insight into the physiological

functions of PDGF through genetic studies in mice. 

Am. J. Respir. Cell Mol. Biol. 34, 746–753. (doi:10. 

116. Ding H

113. Han J, Li L, Zhang Z, Xiao Y, Lin J, Li Y. 2006 PDGF-

C participates in branchial arch morphogenesis and 

is down-regulated by retinoic acid. Toxicol. Lett. 

166, 248–254. (doi:10.1016/j.toxlet.2006.07.308)

112. Zhu C, He L, Zhou X, Nie X, Gu Y. 2016 Sulfatase 2 

is down-regulated by TGF-β in fibroblasts.

119. Xu X, Bringas Jr P, Soriano P, Chai Y. 2005 PDGFR-

β participates in branchial arch morphogenesis and PDGFR-(alpha) deficient mice implicates a novel mesenchymal structure with putative instructive properties in villus morphogenesis. Development 127, 3457–3466.

121. Tallquist MD, Soriano P. 2003 Cell autonomous requirement for PDGF(R)alpha in populations of cranial and cardiac neural crest cells. Development 130, 507–518. (doi:10.1242/dev.00241)

124. Karlsson L, Lindahl P, Heath JK, Betsholtz C. 2000 Abnormal gastrointestinal development in PDGF-A and PDGFR-(alpha) deficient mice implicates a novel mesenchymal structure with putative instructive properties in villus morphogenesis. Development 127, 3457–3466.

126. Nguyen PT et al. 2011 Cognitive and socio-emotional deficits in platelet-derived growth factor receptor-β gene knockout mice. PLoS ONE 6, e18004. (doi:10.1371/journal.pone.0018004)

127. Gao B et al. 2019 Macrophage-lineage TRAP+ cells recruit pericyte-permitted cells for periostal osteogenesis and regeneration. J. Clin. Invest. 129, 2578–2594. (doi:10.1172/jci98857)

130. Zhao J, Urakawa S, Matsumoto J, Li R, Ishii Y, Sasahara M, Peng Y, Ono T, Nishijio H. 2013 Changes in Otx2 and parvalbumin immunoreactivity in the superior colliculus in the platelet-derived growth factor receptor-β knockout mice. BioMed Res. Int. 2013, 842865. (doi:10.1155/2013/842865)

133. Nakamura T, Matsumoto J, Takakura Y, Ishii Y, Sasahara M, Ono T, Nishijio H. 2015 Relationships among parvalbumin-immunoreactive neuron density, phase-locked gamma oscillations, and autistic/schizophrenic symptoms in PDGF-β knock-out and control mice. PLoS ONE 10, e0119258. (doi:10.1371/journal.pone.0119258)

136. Gao Z et al. 2005 Deletion of the PDGF-beta gene affects key fibroblast functions important for wound healing. J. Biol. Chem. 280, 9375–9389. (doi:10.1074/jbc.M413081200)

139. Soriano P. 1997 The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. Development 124, 2691–2700.

140. Yu J, Mu J, Guo Q, Yang L, Zhang J, Liu Z, Yu B, Zhang T, Xie J. 2017 Transcriptomic profile analysis of mouse neural tube development by RNA-Seq. IUBMB Life 69, 706–719. (doi:10.1002/iub.1653)

143. Ishii Y et al. 2006 Mouse brains deficient in PDGF receptor-beta develop normally but are vulnerable to injury. J. Neurochem. 98, 588–600. (doi:10.1111/j.1471-4159.2006.03922.x)

146. Zhuo Y, Hoyle GW, Shan B, Levy DR, Lasky JA. 2006 PDGF-D expression is down-regulated by TGF-β in fibroblasts.

149. Betsholtz C, Eriksson U, Lawrence DA. 2012 Platelet-derived growth factor C deficiency in C57Bl/6 mice leads to abnormal cerebral vascularization, loss of neuroependymal integrity, and ventricular abnormalities. Am. J. Pathol. 180, 1136–1144. (doi:10.1016/j.ajpath.2011.12.006)

152. Lim BJ, Lee WK, Lee HW, Kim JK, Chang HY, Lee JI. 2018 Selective deletion of hepatocyte growth factor receptor-beta-knockout mice. Am. J. Physiol. Heart Circ. Physiol. 317, H330–H344. (doi:10.1152/ajpheart.00054.2019)

155. Sasahara M, Ono T, Nishijo H. 2015 Relationships among parvalbumin-immunoreactive neuron density, phase-locked gamma oscillations, and autistic/schizophrenic symptoms in PDGF-β knock-out and control mice. PLoS ONE 10, e0119258. (doi:10.1371/journal.pone.0119258)

158. Gao Z et al. 2005 Deletion of the PDGF-beta gene affects key fibroblast functions important for wound healing. J. Biol. Chem. 280, 9375–9389. (doi:10.1074/jbc.M413081200)

161. Onogi Y et al. 2017 PDGFRβ regulates adipose tissue expansion and glucose metabolism via vascular remodeling in diet-induced obesity. Diabetes 66, 1008–1021. (doi:10.2337/db16-0881)

164. Popova AP et al. 2014 Reduced platelet-derived growth factor receptor expression is a primary feature of human bronchopulmonary dysplasia. Am. J. Physiol. Lung Cell. Mol. Physiol. 307, L231–L239. (doi:10.1152/ajplung.00342.2013)
185. Salha S, Gehmert S, Brébant V, Anker A, Loibl M, Prantl L, Gehmert S. 2018 PDGF-regulated migration of mesenchymal stem cells towards malignancy acts via the PI3 K signaling pathway. Clin. Hemorheol. Microcirc. 70, 543–551. (doi:10.3233/ch-189319)

186. Dimmeler S. 2005 Platelet-derived growth factor CC—a clinically useful angiogenic factor at last? N. Engl. J. Med. 352, 1815–1816. (doi:10.1056/NEJMcibr050670)

187. Wong RC, Tellis I, Jamshidi P, Pera M, Pébay A. 2007 Anti-apoptotic effect of sphingosine-1-phosphate and platelet-derived growth factor in human embryonic stem cells. Stem Cells Dev. 16, 989–1001. (doi:10.1089/scd.2007.0057)

188. Xu T, Liu N, Shao Y, Huang Y, Zhu D. 2019 MiR-218 regulated cardiomyocyte differentiation and migration in mouse embryonic stem cells by targeting PDGF. J. Cell. Biochem. 120, 4355–4365. (doi:10.1002/jcb.27721)

189. Pereira LA et al. 2012 Pdgfrα and Flk1 are direct target genes of Mix11 in differentiating embryonic stem cells. Stem Cell Res. 8, 165–179. (doi:10.1016/j.scr.2011.09.007)

190. Nishikawa SI, Nishikawa S, Hirashima M, Matsuyoshi N, Kodama H. 1998 Progressive lineage analysis by cell sorting and culture identifies FLK1+VE-cadherin+ cells at a diverging point of endothelial and hematopoietic lineages. Development 125, 1747–1757.

191. Shimizu N et al. 2008 Cyclic strain induces mouse embryonic stem cell differentiation into vascular smooth muscle cells by activating PDGF receptor beta. J. Appl. Physiol. (1985) 104, 766–772. (doi:10.1152/japplphysiol.00870.2007)

192. Dobbin E, Graham C, Corrigan PM, Thomas K, Freeburn RW, Wheeldon H. 2009 Tel/PDGFRbeta induces stem cell differentiation via the Ras/ERK and STAT5 signaling pathways. Exp. Hematol. 37, 111–121. (doi:10.1016/j.exphem.2008.09.012)