



Contents lists available at ScienceDirect

## Molecular Aspects of Medicine

journal homepage: [www.elsevier.com/locate/mam](http://www.elsevier.com/locate/mam)

## PDGF/PDGFR axis in the neural systems

Susmita Sil, Palsamy Periyasamy, Annadurai Thangaraj, Ernest T. Chivero, Shilpa Buch\*

Department of Pharmacology and Experimental Neuroscience, 985880 Nebraska Medical Center, University of Nebraska Medical Center, Omaha, NE 68198, USA

## ARTICLE INFO

## Article history:

Received 13 September 2017

Received in revised form

8 December 2017

Accepted 22 January 2018

Available online xxx

## ABSTRACT

Platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are expressed in several cell types including the brain cells such as neuronal progenitors, neurons, astrocytes, and oligodendrocytes. Emerging evidence shows that PDGF-mediated signaling regulates diverse functions in the central nervous system (CNS) such as neurogenesis, cell survival, synaptogenesis, modulation of ligand-gated ion channels, and development of specific types of neurons. Interestingly, PDGF/PDGFR signaling can elicit paradoxical roles in the CNS, depending on the cell type and the activation stimuli and is implicated in the pathogenesis of various neurodegenerative diseases. This review summarizes the role of PDGFs/PDGFRs in several neurodegenerative diseases such as Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, brain cancer, cerebral ischemia, HIV-1 and drug abuse. Understanding PDGF/PDGFR signaling may lead to novel approaches for the future development of therapeutic strategies for combating CNS pathologies.

Published by Elsevier Ltd.

## 1. Introduction

Platelet-derived growth factor (PDGF) is a family of cysteine-knot-type growth factors that are synthesized in several cells including the brain cells such as the neuronal progenitors, neurons, astrocytes, and oligodendrocytes. PDGF acts in both an autocrine and a paracrine manner and exerts active roles in embryonic development up until adulthood. The PDGF family comprises of five functional subunits, which are disulfide-linked homo- or heterodimers of A-, B-, C-, and D-polypeptide chains, i.e., PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD (Heldin and Westermark, 1999; Kazlauskas, 2017). These growth factors prompt their biological functions on cells through binding with their cognate receptors, namely, PDGF receptor (PDGFR)- $\alpha$ , and PDGFR- $\beta$ , via the receptor tyrosine kinase activity. Binding of PDGF stimulates PDGFR dimerization, which further initiates intracellular signaling. PDGFR- $\alpha$  has been shown to bind to the A-, B-, and C-chains of PDGF, while PDGFR- $\beta$  binds only to the PDGF-BB- and DD-chains (Andrae et al., 2008; Chen et al., 2013a; Kazlauskas, 2017).

Although the mitogenic activity of PDGFs has been well-studied in various cell types, the function of these factors in the central nervous system (CNS), remains less well understood. PDGF-AA has

been shown to function as a potent mitogen for oligodendrocyte progenitors. Interestingly, PDGF-AA null mice that survived postnatally were shown to develop tremors due to severe CNS demyelination (Betsholtz, 2004; Fruttiger et al., 1999). PDGF-BB has been demonstrated to protect primary hippocampal neurons from glutamate-induced neuronal injury by upregulation of PDGFR- $\beta$  signaling, exclusively targeting the NR2B receptors (Beazely et al., 2009). Numerous reports have demonstrated the neuroprotective potential of PDGFs via protection of neuronal/brain cells from direct *in vitro* glutamate-induced excitotoxicity and hypoxic-ischemic injury (Egawa-Tsuzuki et al., 2004; Ishii et al., 2006; Tseng and Dichter, 2005). Moreover, PDGFs and PDGFR activation are also vital for neuronal progenitor cell differentiation into neurons (Erlandsson et al., 2001; Williams et al., 1997) and have also been reported to guard hippocampal neurons against oxidative insults and energy deprivation (Cheng and Mattson, 1995). In recent years, PDGF-CC has emerged as a new player for its potential therapeutic efficacy in various neurodegenerative diseases such as Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS) reviewed in (Lee et al., 2013). This review aims to unravel the role of PDGF/PDGFR signaling in various CNS cell types such as the neurons, microglia, astrocytes, oligodendrocytes as well as also focusing on the importance of this axis in various neurodegenerative diseases.

\* Corresponding author.

E-mail address: [sbuch@unmc.edu](mailto:sbuch@unmc.edu) (S. Buch).

**Abbreviations**

AD	Alzheimer disease
APP	Amyloid precursor protein
ALS	Amyotrophic lateral sclerosis
BBB	Blood-brain barrier
cART	Combined anti-retroviral therapy
CNS	Central nervous system
CSF	Cerebrospinal fluid
FGF-2	Fibroblast growth factor-2
GSK-3 $\beta$	Glycogen synthase kinase 3 $\beta$
HAND	HIV-1 associated neurocognitive disorders
HD	Huntington disease
HIV-1	Human immunodeficiency virus-1

LRP1	Low-density lipoprotein receptor-related protein 1
PDGF	Platelet-derived growth factor
MCP-1	Monocyte chemoattractant protein-1
NMDA	N-methyl-D-aspartate
NPC	Neural precursor cell
PD	Parkinson disease
PI3K	phosphatidylinositol-3-kinase
SIV	Simian immunodeficiency virus
Tat	Transactivator of transcription
TRPC1	Transient receptor potential cation channel subfamily C member 1
tPA	Tissue plasminogen activator
VEGF	Vascular endothelial growth factor
VSMCs	Vascular smooth muscle cells

**2. Neurons**

PDGFRs are expressed in the neural system during development. Both PDGFR- $\alpha$  and PDGFR- $\beta$  are expressed by different neuronal cell types such as the dopaminergic neurons in the substantia nigra, cortical neurons, striatal neurons, neurospheres, retinal ganglion cells and neuronal cells in the inner/outer nuclear layers of the retina (Nait Oumesmar et al., 1997). It has been shown by Tang et al. (2010) that neurons are important cellular targets of PDGF-CC. PDGF-C treatment either via protein exposure or gene delivery approaches was able to exert neuroprotective effects in both the retina as well as in neurons. PDGF-C treatment of various neuronal cell types also inhibited oxidative stress, neurotoxin production, and neuronal apoptosis via modulation of glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) activity both *in vivo* as well as *in vitro* (Tang et al., 2010). Reciprocally, PDGF-CC null mice showed increased neuronal death (Tang et al., 2010).

It has been shown that during ischemia there is increased expression of PDGF-A and -B mRNA and PDGF-BB and PDGF-AB protein levels in neurons, thereby implicating these ligands in the damaged brain areas, play an essential role in neuronal survival (Krupinski et al., 1997). In another study, it has been shown that exogenously administered PDGF-BB exhibited neuroprotective effects during focal ischemia (Sakata et al., 1998), while also preventing glutamate and N-methyl-D-aspartate (NMDA)-induced hippocampal neuronal death (Egawa-Tsuzuki et al., 2004; Tseng and Dichter, 2005). Furthermore, it has also been demonstrated that serotonin receptor agonist treatment prevented NMDA-induced cell death, which in turn, was mediated through increased expression of PDGFR- $\beta$  in primary hippocampal neurons (Vasefi et al., 2012, 2013). In another study, Chao et al. (2014) reported that human immunodeficiency virus-1 (HIV-1) Transactivator of transcription (Tat) protein-mediated impairment of neural precursor cell (NPC) proliferation was ameliorated by PDGF-BB via the activation of the p38 and c-Jun-N-terminal kinases/mitogen activated protein kinases (JNK/MAPK) pathways. Interestingly, a novel GSK-3 $\beta$ /catenin pathway has also been implicated in PDGF-BB-mediated neurogenesis.

Studies have also reported that in human neuroblastoma cells PDGF-BB exerts neuroprotection against HIV-1 envelope glycoprotein, gp120-mediated apoptosis via activation of the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathways (Peng et al., 2008). In rat hippocampal neurons, PDGF-BB has been shown to regulate the expression of Arc/Arg3.1 gene via activation of the MAPK/extracellular signal regulated kinase (ERK) pathway and thus has implication in both synaptic plasticities as well as long term potentiation (Peng et al., 2010). In recent years, it has elegantly

been demonstrated that alterations in PDGF-CC levels and its signaling can exert a robust neuroprotective effect in a multitude of neurodegenerative disease models such as PD (Tang et al., 2010), ALS (Lewandowski et al., 2016b), stroke (Su et al., 2008), retinitis pigmentosa (He et al., 2014), focal retinal degeneration (Wang et al., 2014), glaucoma (Tang et al., 2010), HIV-associated dementia (Peng et al., 2012) and macular degeneration (Hou et al., 2010; Lee et al., 2013), thereby underscoring its potential as a therapeutic target.

**3. Astrocytes**

Astrocytes, the most abundant type of glial cells in the brain, are not only critical for neuronal support, but also play key roles in CNS homeostasis by exerting a multitude of vital functions such as neurotransmission (Hansson and Ronnback, 1995), metabolite and electrolyte homeostasis (Chih and Roberts, 2003; Kofuji and Newman, 2004; Auestad et al., 1991), cell signaling (Kirchhoff et al., 2001), inflammation (Colombo and Farina, 2016), and synapse formation and function (Clarke and Barres, 2013). These cells are the main players in providing neuronal nourishment by secreting chemokines and growth factors, controlling the chemical composition surrounding the neurons and by providing physical and structural support for cerebral capillaries. In reactive astrogliosis, cerebral insults lead to morphological and functional impairments in astrocytes, and this has been reported to play a significant role in the pathogenesis underlying various neurodegenerative diseases such as AD, ALS, Epilepsy, Huntington disease (HD), and Ischemia/stroke and PD (Liu et al., 2017). Activation of PDGF/PDGFR signaling plays a major role in astrocytic cellular functions including regulation of metabolic activity, cell differentiation, regulation of neurotransmitters, thereby underscoring the role of these cells in the development of CNS, cognitive functioning and neuroprotection (Cabezas et al., 2016).

The effects of PDGF-AA and its role in glial cell differentiation has been well documented (Raff et al., 1988; Richardson et al., 1988). Several reports have shown that PDGFs can induce PDGF responsive neural precursor cells to differentiate into oligodendrocytes, neurons and astrocytes to a lesser extent (Chojnacki et al., 2008; Chojnacki and Weiss, 2004; Jackson et al., 2006). PDGF secreted by type-1 astrocytes has been known to stimulate the proliferation and differentiation of oligodendrocyte progenitor cells into oligodendrocytes and type-2 astrocytes. In oligodendrocytes, PDGFs not only plays a role in differentiation but is also critical for migration to specific sites via activation of PDGFR- $\alpha$  (Fernandovalenzuela et al., 1997; Richardson et al., 1988). It must be noted that astrocyte migration induced via PDGFR- $\alpha$ -mediated signaling is vital for maintaining cerebral microvasculature (Itoh

et al., 2011). Several lines of evidence indicate that PDGFR- $\alpha$  signaling is also important for astrocyte network formation during neural retina development (Fruttiger et al., 1996; Mudhar et al., 1993).

#### 4. Microglia

Microglia, a type of small macrophage-like glial cells within the CNS, that are actively involved in immune responses like phagocytosis and inflammation have also been shown to secrete PDGFs (Nicholas et al., 2001; Su et al., 2017). In another study, it has been reported that depending on the state of activation; microglia produces soluble factors that promote oligodendrocyte development via the PDGFR- $\alpha$  signaling (Nicholas et al., 2001). It has been shown that application of vascular endothelial growth factor (VEGF) and PDGF at the same time as a stab injury to the rat brain initially delayed the inflammatory response up to day 5, but thereafter evoked a persistent astrogliosis and microglial response up to 60 days (Norazit et al., 2011). It has been suggested that following spinal cord injury treatment with growth factors such as PDGF and VEGF significantly decreased the numbers of activated/primed cells while increasing the numbers of phagocytic microglia (Lutton et al., 2012). More recently, it has been reported that in acute ischemic stroke thrombolytic tissue plasminogen activator (tPA) treatment on the parenchymal side of the neurovascular unit increased BBB permeability and improved neurological outcomes via activation of the PDGF-C/PDGFR- $\alpha$  axis (Su et al., 2017). Furthermore, in this study it was also suggested that tPA-induced the expression of integrin Mac-1 in microglia/macrophages, which acts in concert with the endocytic receptor low-density lipoprotein receptor-related protein 1 (LRP1), thereby promoting PDGF-C signaling and controlling BBB permeability (Su et al., 2017).

#### 5. Oligodendrocytes

Oligodendrocytes, the myelinating cells of the CNS originate from oligodendrocyte progenitors and are known to secrete and respond to numerous key proliferative, survival, and protective factors including but not limited to VEGF, fibroblast growth factor-2 (FGF2), and PDGFs (He and Lu, 2013; Pfeiffer et al., 1993). In addition to pericytes and astrocytes, oligodendrocytes abundantly express PDGFRs. Deficiency of PDGFR- $\alpha$  has been shown to impair proliferation and regeneration of oligodendrocytes under pathological conditions implicating thereby the potential role of PDGF-C/PDGFR- $\alpha$  in oligodendrocyte maturation and axonal myelination (Murtie et al., 2005). In another study, substantial oligodendrocyte death and subsequent demyelination following spinal cord injury were rescued after transplantation of PDGF-responsive neural precursors in the spinal cord of rats. One-third of the surviving PDGF-responsive neural precursors developed into anti-adenomatous polyposis coli clone CC1 expressing mature oligodendrocytes which, in turn, produced compact myelin sheaths with normal periodicity, although insufficient to produce behavioral improvements (Plemel et al., 2011). In another study, stromal-derived PDGF-C was found to be a crucial factor in the recruitment and activation of oligodendrocyte progenitor cells and was involved in the progression of gliomas in the brain (Huang et al., 2014).

#### 6. Spinal cord

Among the PDGFs, PDGF-CC is ubiquitously expressed in multiple tissues including the brain and spinal cord. In *Gekko japonicus*, it was shown that expression levels of this factor were increased after tail amputation and was associated with spinal cord injury

and regeneration (Liu et al., 2009). In another study, Ding et al. (2004) have shown that knocking out PDGF-CC (*Pdgfc*<sup>(-/-)</sup>) resulted in mice lethality owing to difficulties in feeding, breathing, and defects in the formation of the complete cleft of the secondary palate and distorted dorsal spinal cord in the lower spine. Lewandowski et al. (2016a) reported that PDGF-CC mRNA transcript was strongly expressed in the cells of spinal cord tissue, primarily in a subpopulation of ChAT + neuronal cells as evidenced by the location of  $\beta$ -galactosidase activity in *Pdgfc*<sup>(-/-)</sup>/*lacZ* mice. Further, it has been reported in the spinal cords of presymptomatic SOD1G93A mice; there was increased expression of tPA leading to proteolytic cleavage of PDGF-CC protein, which in turn, results in accumulation of cleaved 22-kDa PDGF-CC protein with a ligand-dependent activation of PDGFR- $\alpha$ . While there are reports on the expression and effects of PDGF-CC in the spinal cord, there is a paucity of information on the role of other members of the PDGF family in the spinal cord.

#### 7. Blood-brain barrier

BBB separates the parenchyma from circulating blood and extracellular fluid in the brain and comprises of non-fenestrated tightly-joined endothelial cells with tight junctions, thick basement membranes, and astrocytic glial end-feet. BBB integrity and its function is thus tightly regulated by endothelial cells, pericytes, and astrocytes. BBB restricts the diffusion of microscopic objects and large or hydrophilic molecules into the cerebrospinal fluid (CSF) while allowing the diffusion of small hydrophobic molecules, such as oxygen, hormones, and carbon dioxide (Abbott et al., 2010; Lee et al., 2013). It is well recognized that both the neural and vascular cells express PDGF ligands as well as the receptors, and that signaling via PDGF receptor activation plays critical roles in both the physiology as well as pathology of the CNS.

PDGF/PDGFR signaling is associated with a breach of the BBB and underlies stroke as well as life-threatening CNS edema (Funa and Sasahara, 2014). Indeed, several lines of evidence have implicated a significant role of PDGFR- $\alpha$  and PDGFR- $\beta$  in the neurovascular unit and BBB permeability. Expression of PDGF-BB, for example, has been demonstrated in vascular endothelial cells while PDGFR- $\beta$  is expressed in pericytes and vascular smooth muscle cells (Hellstrom et al., 1999). Recently, it has been shown that *Pdgfr* $\beta$ F7/F7 mutant mice with disrupted PDGFR- $\beta$  signaling showed an early and progressive region-dependent loss of brain pericytes and vascular smooth muscle cells (VSMCs) in the developing brain, leading to an aggressive and rapid microvascular phenotype without the early involvement of VSMCs (Nikolakopoulou et al., 2017).

It was shown by Su et al. (2008) that there was increased BBB permeability following intraventricular injection of PDGF-CC protein in mice brain. Furthermore, PDGF-C/PDGFR- $\alpha$  signaling was involved in the loss of BBB function during the stroke, and interestingly, pharmacological inhibition of PDGF signaling with the receptor antagonist imatinib or with neutralizing antibodies to PDGF-CC, significantly improved BBB integrity (Su et al., 2008, 2015). Studies by Ma et al. (2011) have reported that BBB impairment following intracerebral hemorrhage occurs via PDGFR- $\alpha$  signaling involving p38 MAPK-mediated matrix metalloproteinase activation, thereby underscoring the role of these signaling pathways in this process. Recently, Sagare et al. (2015) reported a correlative link between elevated levels of soluble PDGFR- $\beta$  in cell culture supernatants and loss of cell-associated PDGFR- $\beta$  in pericytes. Since BBB disruption and increased permeability positively correlate with high levels of soluble PDGFR- $\beta$  in the CSF in patients with mild dementia, soluble PDGF-BB was suggested as a potential biomarker of brain pericyte injury and BBB dysfunction (Sagare

et al., 2015).

Niu et al. (2014) reported that exposure of pericytes to HIV-1 Tat protein resulted in increased expression of PDGF-BB, which in turn, led to decreased pericyte coverage with a subsequent breach of the BBB. Furthermore, Yao et al. (2011a) have also demonstrated that exposure of human brain microvascular endothelial cells or mice to cocaine resulted in increased permeability of the endothelial barrier, and this was abrogated by exogenous administration of PDGF-BB neutralizing antibodies, thereby further underscoring the role of PDGF/PDGFR axis in BBB disruption and permeability.

## 8. Role of PDGF and its receptors in CNS development and vascularisation

PDGFs/PDGFRs are expressed in the CNS both during developmental and adult stages. Studies using mutant mice have demonstrated the essential roles of PDGFs during development suggesting regulation of glial and neuronal progenitor cells. Interestingly, PDGFRA<sup>-/-</sup> mice die at mid-gestation due to aortic arch and cleft palate defects or neural crest defects (Funa and Sasahara, 2014; Schattman et al., 1992; Soriano, 1997) while PDGFRB<sup>-/-</sup> mice die at birth likely due to ventricular septal, hematopoiesis and blood vessel formation defects (Hellstrom et al., 1999; Leveen et al., 1994; Lindahl et al., 1997; Richarte et al., 2007). Studies using mice with ligand knockouts have also revealed that PDGFA<sup>-/-</sup> mice die mid-gestation while those that survive showed defect in lung development (Bostrom et al., 2002). On the other hand, mice deficient for PDGF-BB exhibited renal, cardiovascular as well as hematological abnormalities (Hellstrom et al., 1999; Leveen et al., 1994; Lindahl et al., 1997). PDGF-CC deficient mice exhibited postnatal lethality due to developmental defects (Ding et al., 2004). Recently, the essential role of PDGF-CC/PDGFR- $\alpha$  has been shown for the formation of the intact meningeal layer around the mouse cerebrum, and its deficiency led to secondary brain developmental defects (Andrae et al., 2016). For example, the brains from newborn *Pdgfr<sup>c</sup>*<sup>-/-</sup> and *Pdgfr<sup>c</sup>*<sup>GFP/+</sup> double mutant mice pups exhibited several CNS defective phenotypes including spina bifida, irregular shape of cerebral hemispheres, reduced cerebellum size, and significant differences in an interhemispheric fissure. In these *Pdgfr<sup>c</sup>*<sup>-/-</sup> and *Pdgfr<sup>c</sup>*<sup>GFP/+</sup> double mutant mice pups neuronal over-migration and decreased the density of the vasculature in the meninges were the likely underlying causes for abnormalities and regional loss of basement membrane integrity at the brain surface (Andrae et al., 2016). Previously, Fredriksson et al. (2012) have also reported that deficiency of PDGF-CC in C57BL/6 mice showed abnormal cerebral vascularisation and ventricular malformations with distorted ependymal lining and congenital defects. Similar studies by Stefanitsch et al. (2015) have reported that ablation of tPA, an activating enzyme for PDGF-CC, also resulted in cognitive deficits and defective vascularisation, strongly supporting the role of PDGF-CC signaling during CNS development. These studies suggest that activation of PDGFs signaling could thus be developed as a potential therapeutic strategy for preventing CNS developmental defects (Andrae et al., 2008) (see Table 1).

## 9. Role of PDGF in neurological disorders

### 9.1. Alzheimer disease

AD is a progressive neurodegenerative disease that is characterized by dementia and personality changes (Huberman et al., 1994; Jellinger and Bancher, 1996). The pathological hallmarks of the disease are accumulation of amyloid beta and hyperphosphorylated Tau proteins. Since A $\beta$  accumulation begins decades before symptoms actually manifest, it has been suggested

that biomarkers in the plasma and CSF, could likely indicate the initiation of disease process much before the actual neurodegeneration process and, can thus be tapped for therapeutic advantage. It is well realized that plasma is much easier to obtain than CSF for biomarker testing. In another study, among the different 18 plasma markers studied, PDGF-BB was considered as one of the most important biomarkers associated with AD (Ray et al., 2007). The declining levels of plasma PDGF-BB correlated with mild cognitive impairments observed in AD patients (Bjorkqvist et al., 2012). PDGF-BB was thus indicative of a useful biomarker in presymptomatic individuals with mild cognitive impairment (Bjorkqvist et al., 2012). Along the same lines, it was shown in postmortem AD brains that levels of PDGF-BB in neurons correlated with the patterns of synaptic loss and sprouting while immunostaining for PDGF-AA in the vessels correlated with glial proliferation (Masliah et al., 1995). It has been reported by several groups that levels of both plasma and CSF PDGF-BB and soluble PDGFR- $\beta$  were increased in AD patients, thus reflecting not only pericyte injury but also dysfunction of the PDGF-BB/PDGFR- $\beta$  axis (Sagare et al., 2013, 2015). In AD transgenic mice, deficiency of PDGFR- $\beta$  signaling resulted in pericyte loss leading to BBB disruption, underlying the neurodegenerative changes independent of amyloid- $\beta$  (Winkler et al., 2014). On the other hand, studies in mice overexpressing amyloid- $\beta$  precursor protein (APP) crossed with pericyte-deficient (*Pdgfrb*<sup>+/-</sup>) mice (*APP<sup>Sw/0</sup>;Pdgfrb*<sup>+/-</sup> mice) indicated that defective PDGF-BB-PDGFR- $\beta$  signaling resulted in faulty amyloid- $\beta$  clearance from brain interstitial fluid by diminishing LRP1-mediated amyloid- $\beta$  clearance in pericytes culminating into cerebral amyloid angiopathy (Sagare et al., 2013). Accelerated pericyte degeneration in *APP<sup>Sw/0</sup>;Pdgfrb*<sup>+/-</sup> mice also leads to tau pathology and neuronal loss, which is not normally seen in *APP<sup>Sw/0</sup>* mice (Sagare et al., 2013). These data suggest that a two-hit (vascular and amyloid- $\beta$ ) phenomenon is essential for the development of full-spectrum of AD-like pathology in mice. Whether a similar two-hit process contributes to the pathogenesis of late-onset AD in humans, which is characterized by pericyte degeneration (Sweeney et al., 2016), remains unclear. Moreover, it has been shown that PDGF-BB binds to sorL1, sorCS1 and sorCS3 (Gliemann et al., 2004; Hermey et al., 2006), which in turn, could influence its interaction and downstream signaling from PDGFR- $\beta$ , that ultimately could lead to pericyte dysfunction and/or degeneration, an observation in late-onset AD (Baloyannis and Baloyannis, 2012; Farkas and Luiten, 2001; Halliday et al., 2016; Montagne et al., 2015; Sengillo et al., 2013; Sweeney et al., 2016). In addition to PDGF-BB, sorL1 binds other LRP1 ligands analogous to LRP1, which could influence LRP1-mediated BBB clearance (Zlokovic et al., 2010). More studies are needed to evaluate the effects of PDGF-BB interactions with sorL1 and sorCS1–3 in downstream PDGFR- $\beta$  signaling in pericytes to understand whether these Vps10 proteins can be a molecular link between AD and the pathogenesis of diabetes. Another study has also shown that the APP can be cleaved by PDGF-BB via the  $\gamma$ -secretase dependent pathway (Gianni et al., 2003). Additional vital role of PDGF in AD has also been reported wherein neurogenesis was observed in the subventricular zone or dentate gyrus subgranular zone in the PDGF-APP(Sw,Ind) mice brain (Jin et al., 2004). Taken together these studies underscore the role of PDGF-BB in AD and its implication as a therapeutic target.

### 9.2. Parkinson disease

PD is a neurodegenerative brain disorder that is accompanied by intracellular inclusions of  $\alpha$ -synuclein, neuronal loss in the substantia nigra and striatal dopamine deficiency leading to motor deficits including intentional tremors (Alexander, 2004). It afflicts



**Table 1**

Physiological roles of PDGFs/PDGFRs in the cells of CNS.

Cell types/Tissues	Isoforms involved	Regulation	Outcome	Model	References
Neurons	PDGF-BB	Up	Increased mRNA & protein levels in damaged brain areas	Postmortem brain from ischemic stroke patients	(Krupinski et al., 1997)
	PDGF-AB				
	PDGF-CC	NA	Neuroprotective	Retina and neurons	(Tang et al., 2010)
	PDGF-BB	NA	Neuroprotective	Rat	(Egawa-Tsuzuki et al., 2004)
	PDGF-BB	NA	Neurogenesis	Neural precursor cells	(Chao et al., 2014)
	PDGF-BB	NA	Neuroprotection	Neuroblastoma cells	(Peng et al., 2008)
Astrocytes	PDGF-BB	NA	Synaptic plasticity & long-term potentiation	Rat hippocampal neurons	(Peng et al., 2010)
	PDGFR $\beta$	NA	Prevented NMDA-induced cell death	Primary hippocampal neurons	(Vasefi et al., 2013)
	PDGF/PDGFR	NA	Cognitive functioning & neuroprotection	Astrocytes	(Cabezas et al., 2016)
	PDGFR $\alpha$	NA	stimulate the proliferation and differentiation of oligodendrocyte progenitor cells into oligodendrocytes and type-2 astrocytes.	Type 1 astrocytes	(Valenzuela et al., 1997)
Microglia	PDGFR $\alpha$	NA	Astrocyte migration & maintenance of cerebral microvasculature.	Astrocytes	(Fruttiger et al., 1999; Itoh et al., 2011)
	PDGF	NA	Astrocyte network formation during neural retina development	NA	
	PDGF-C/axis	NA	Oligodendrocyte development	Rats	(Nicholas et al., 2001)
	PDGFR- $\alpha$	NA	Persistent astrogliosis and microglial response	Mice	(Norazit et al., 2011)
Oligodendrocytes	PDGF-C/axis	NA	BBB permeability and improved neurological outcomes	Mice	(Su et al., 2017)
	PDGFR- $\alpha$	NA	Impair proliferation and regeneration of oligodendrocytes	Rats	(Lee et al., 2013)
	PDGF-C	NA	Recruitment and activation of oligodendrocyte progenitor cells and progression of gliomas	Mice	(Huang et al., 2014)
Spinal cord	PDGF-CC	Knockout	Lethality and defects in the formation of the complete cleft of the secondary palate and distorted dorsal spinal cord in the lower spine	Mice	(Ding et al., 2004)
Blood-brain barrier	PDGF-BB	Up	BBB dysfunction in the embryo and adult brains.	Endothelial cells and pericytes	(Armulik et al., 2010; Hellstrom et al., 1999)
	PDGF-CC	NA	Loss of BBB function during stroke	Mice	(Su et al., 2008)
	PDGF-BB	Up	HIV Tat-mediated decreased pericyte coverage with a subsequent breach of the BBB.	Pericytes	(Niu et al., 2014)
CNS development & vascularisation	PDGF-BB	NA	Cocaine-mediated increased permeability of the endothelial barrier	Endothelial cells and mice	(Yao et al., 2011a)
	PDGFR $\alpha$	Knockout	Death at mid-gestation	PDGFR $\alpha$ (–/–) mice	(Funa and Sasahara, 2014; Schatteman et al., 1992; Soriano, 1997)
	PDGFR $\beta$	Knockout	lethal	PDGFR $\beta$ (–/–) mice	(Hellstrom et al., 1999; Leveen et al., 1994; Lindahl et al., 1997; Richarte et al., 2007)
	PDGF-CC	Knockout	Postnatal lethality due to developmental defects	PDGF-CC (–/–) mice	(Ding et al., 2004)
	PDGF-CC	Down	Cognitive deficits & defective vascularisation during CNS development	Adult tPA deficient mice	(Stefanitsch et al., 2015)

almost 10 million people worldwide and has serious health and economic burden. There is an urgent need in the field for development of regenerative treatment(s) that can halt or reverse the disease progression. In this regard, several growth factors have been examined for their therapeutic efficacy, for restoration of the dopaminergic nigrostriatal pathway damaged in this disease. PDGF-BB is one such candidate that was recently investigated in a phase-1 clinical trial wherein the findings demonstrated a dose-dependent increase in dopamine transporter binding in the putamen of PD patients (Paul et al., 2015). In another study, Zachrisson and colleagues reported that intracerebroventricular administration of PDGF-BB in a 6-hydroxydopamine medial forebrain bundle lesion mouse model of PD, restored striatal dopamine transporter binding sites leading, in turn, to reversal of behavioral impairment. In this study, PDGF-BB was shown to mediate its protective response by promoting proliferation of neural progenitor cells in the subventricular zone (Zachrisson et al., 2011). Similar to findings by Zachrisson et al. (2011), in a partial 6-hydroxydopamine medial forebrain bundle lesion mouse model of PD (Padel et al., 2016), PDGF-BB protected against behavioral impairment and this was

accompanied by restoration of the nigrostriatal pathway as well as inhibition of pericyte activation. Considering the neuroprotective effects of PDGF-BB in animal models of PD, clinical trials were conducted on PD patients with recombinant human PDGF-BB (rhPDGF-BB). Twelve patients with moderate PD received rhPDGF-BB via an implanted drug infusion pump and an investigational i.c.v. catheter. Results showed that rhPDGF-BB at all doses was well tolerated and there were no adverse effects of rhPDGF-BB on the PD patients. This study also showed that there was a positive effect on dopamine transporter binding in the right putamen in these patients (Paul et al., 2015). Extensive clinical trials are expected to provide further evidence of safety and efficacy of the use of this growth factor in PD. In addition to PDGF-BB, PDGF-AA has also been shown to correlate with levels of plasma  $\alpha$ -synuclein in PD patients, indicating thereby its potential as a biomarker for PD (Lue et al., 2016).

### 9.3. Amyotrophic lateral sclerosis

ALS is a progressive neurodegenerative disease, characterized

by degeneration of motor neurons in the brain and spinal cord resulting in paralysis and ultimately death (Chen et al., 2013b). Only 10% of the ALS affected population are of familial origin while 90% are sporadic (Chen et al., 2013b). Factors associated with sporadic ALS are heterogeneous and poorly understood (Robberecht and Philips, 2013). In one study, elevated levels of PDGF-BB were reported in patients with progressive muscular atrophy and ALS (Furukawa et al., 2015) while in another study, motor neurons of human sporadic ALS patients were shown to have increased expression of PDGF-CC gene and its activator PLAT. In the same study, it has been demonstrated that activation of the PDGF-CC pathway in the SOD1G93A mice – a mouse model of ALS, led to the disruption of the blood-spinal cord barrier and capillary regression (Lewandowski et al., 2016b). In the same model, however, inhibition of PDGF-CC resulted in restoration of blood spinal cord barrier integrity but did not prevent capillary regression during end stage disease. Taken together, it was concluded that PDGF-CC induced blood-spinal cord barrier disruption thereby contributing to the onset of ALS. Contrary to previous findings, it was reported that PDGF treatment restored the soma and nucleus, as well as reduced apoptosis in ALS-CSF, exposed motor neurons (Chen et al., 2014). More studies are required to delineate the role of PDGF family in ALS disease progression, and to identify the mechanism(s) and therapeutic targets for the disease.

#### 9.4. Cerebral ischemia

Ischemic stroke is a cerebrovascular disease resulting from a transient or permanent impairment of cerebral blood flow and is accompanied by a disturbance in cellular homeostasis. Strategies aimed at improving reduced regional cerebral blood supply in time is critical for better stroke outcomes and post-stroke functional recovery. Restoring appropriate blood flow via angiogenesis, thereby facilitating increased delivery of oxygen and nutrients to the affected brain tissue is of paramount importance (Yin et al., 2015). The role of PDGF-B/PDGFR- $\beta$  system in neuroprotection, angiogenesis, and vascular remodeling via endothelial-pericyte crosstalk has been well documented in cerebral ischemia (Renner et al., 2003). Upregulation of PDGF-BB, at the ischemic site, has been observed within 48 h of ischemia, thereby suggesting a role for this factor in vascular remodeling post stroke (Arimura et al., 2012; Renner et al., 2003). It has been speculated that PDGFR- $\beta$  expressed by the brain pericytes as well as in neurons and astrocytes could likely be critical in mediating the neuroprotective role of PDGF-BB. In fact, in a study involving rat middle cerebral artery occlusion model of stroke, it was shown that PDGFR- $\beta$  expression was specifically upregulated in the pericytes in the peri-infarct areas. Interestingly, in this model, PDGF-B was also upregulated in endothelial cells in peri-infarct regions with a strong phosphorylation of Akt in the PDGFR- $\beta$ -expressing pericytes in peri-infarct areas. In the cultured pericytes, PDGF-B induced cell growth and anti-apoptotic responses through Akt. In addition to PDGF-B, these authors also found significantly increased expression of nerve growth factor and neurotrophin-3 involving activation of Akt in pericytes. Thus, the PDGFR- $\beta$ -Akt signaling in brain pericytes may play various important roles leading to neuroprotection after ischemic stroke (Arimura et al., 2012).

PDGFR- $\beta$  signaling is thus crucial for neuroprotection, endogenous tissue repair and functional recovery via its signaling in neurons, pericyte/vascular smooth muscle cells and astrocytes (Shen et al., 2012). Additionally, the role of microglial and neuronal PDGF-B in neuroprotection has also been well documented (Sasahara et al., 1995). In cells under ischemic conditions, PDGF-CC has been shown to mobilize endothelial progenitor cells, induced differentiation of bone marrow cells into endothelial cells; and

stimulated migration of endothelial cells (Li et al., 2005). Interestingly, The association of serum PDGF-CC levels with hemorrhagic transformation and edema was examined in patients with ischemic stroke following treatment with tPA and it was found that patients that developed hemorrhagic transformation in ischemic stroke had higher levels of serum PDGF-CC (Rodriguez-Gonzalez et al., 2013). It has also been reported that the intraventricular injection of tPA or the active form of PDGF-CC, in non-ischemic conditions, resulted in significant increase in cerebrovascular permeability. On the other hand, co-injection of neutralizing antibodies to PDGF-CC with tPA notably blocked the cerebrovascular permeability, thereby indicating that PDGF-CC is a downstream target of tPA within the neurovascular unit. These effects were found to be mediated through the activation of PDGFR $\alpha$  in perivascular astrocytes, and furthermore, treatment of mice with imatinib, the PDGFR $\alpha$  antagonist, following ischemic stroke, reduced both the cerebrovascular permeability as well as hemorrhagic complications associated with late administration of thrombolytic tPA (Su et al., 2008, 2015). Activation of PDGF-CC by tPA *in vitro* however, was inefficient. The mechanism of PDGF-CC activation in the neurovascular unit however, remains elusive. Recently however, it has been shown that tPA-mediated activation of PDGF-CC was mediated via the binding of the integrin Mac-1 (expressed in brain microglia/macrophages) to the endocytic receptor LRP1 in the neurovascular unit (Su et al., 2017). Modulation of PDGF-CC activity could thus provide novel opportunities for treating ischemic diseases. Tapping the PDGF/PDGFR axis for improving angiogenesis, conferring cellular protection, and ameliorating edema, post-cerebral ischemia could thus be a therapeutic strategy.

#### 9.5. Glioblastoma

Glioblastoma is one of the most aggressive forms of malignant brain tumors, that is resistant to all forms of therapy often leading to death within 9–12 months of diagnosis (Lokker et al., 2002). Glioblastomas are associated with numerous genetic alterations affecting cell survival and proliferation. Among the various types of gene alterations in glioblastoma, PDGF-AA is one of the most common ones (Lokker et al., 2002). Consistent with altered PDGF expression, several studies have also shown a role for autocrine PDGFR signaling in glioma cell proliferation (Lokker et al., 2002). Malignant astrocytoma expressed increased levels of PDGF-A and PDGF-B compared with non-neoplastic glia. Expression of PDGFR- $\alpha$  was found to be elevated both in malignant as well as in low-grade astrocytoma. Expression of PDGF and PDGFR in low-grade astrocytoma suggests that activation of PDGF autocrine loops could be an early event in the pathogenesis of malignant astrocytomas (Guha et al., 1995). In glioma cells, increased expression of PDGFR- $\alpha$ , as well as the PDGF-AA and BB proteins, has been reported compared with the astrocytoma (Costa et al., 2012; Hermanson et al., 1992). Furthermore, PDGF-CC and PDGF-DD proteins have also been implied in autocrine glioma signaling (di Tomaso et al., 2009). Consequently, inhibition of cultured glioma cell growth has been achieved with different PDGF-AA antagonists, including dominant negative forms of PDGFs or PDGF receptors (Shamah et al., 1993; Strawn et al., 1994).

*In vivo*, overexpression of PDGF-B in neural progenitors induced the formation of oligodendrogliomas in about 60% of mice; while overexpression of PDGF in astrocytes induced the formation of either oligodendrogliomas or mixed oligoastrocytomas in about 40% of mice (Dai et al., 2001; Uhrbom et al., 1998). Interestingly, overexpression of PDGFs has also been convincingly shown to induce tumors, both in the wild-type animals (marmoset, rat, mouse) as well as in mice with targeted deletions of suppressor genes such as Tp53 or Ink4A (Westermarck, 2014). In another study,

PDGF-BB was shown to downregulate the expression levels of miR-21 and miR-128, which in turn, was associated with increased cell proliferation, suggesting thereby that PDGF-BB could enhance tumor proliferation by modulating the expression of onco-miRs and tumor suppressor miRNAs (Costa et al., 2012). In another study, it was shown that hypoxia inducible factor 1- $\alpha$  (HIF-1 $\alpha$ ) induced the expression of PDGF-B in glioblastoma cell lines (Yoshida et al., 2006). In support of this study it was also observed that PDGF BB induced the secretion of VEGF from U-105MG glioma cell line, thereby underscoring its critical role in angiogenesis (Tsai et al., 1995).

Although most of the studies on gliomas have been performed with PDGF-AA and PDGF-BB, few other studies have also investigated the roles of PDGF-CC and PDGF-DD. For example, studies have reported the abundant expression of PDGF-CC in brain tumor cells and tissues compared to the brains of fetal and normal adults (Lokker et al., 2002). Increased expression of PDGF-CC in human gliomas has been reported to play a major role in glioma maturation and stabilization and could be reversed by anti-VEGF therapy (di Tomaso et al., 2009). Similar to PDGF-CC, PDGF-DD was abundantly expressed in 10 of 11 brain tumor cell lines and 3 of 5 primary brain tumor samples (Lokker et al., 2002). These authors further reported that both PDGF-CC and PDGF-DD regulated glioma cell proliferation via activation of the Akt/Erk/MAPK pathways (Lokker et al., 2002). In another study, it has been shown that tPA and matriptase are major proteases for processing PDGF-C in MCF7 breast cancer cells. Increased PDGF-C expression resulted in cell proliferation, anchorage-independent cell growth and tumor cell motility by autocrine signaling. In addition, PDGF-C produced from MCF7-cells induced fibroblast cell migration via the paracrine loop (Hurst et al., 2012). It was also shown that the expression of PDGF-C and VEGF in endothelial and tumor cells of GBM correlated with HIF-1 $\alpha$  expression. These findings in GBM tumor cells and vessels further reinforced the beneficial role of combined anti-angiogenic approaches to potentially improve the therapeutic response for GBM (Clara et al., 2014). Taken together these findings suggest that the PDGF/PDGFR- $\alpha$  signaling axis within the glioma stromal microenvironment could contribute to vascular remodeling and aberrant tumor angiogenesis in the brain (Huang et al., 2014).

#### 9.6. HIV-1 and drugs of abuse-associated neurological disorders

Despite successful suppression of viremia in the era of combined antiretroviral therapy (cART), chronic inflammation with underlying neurocognitive impairment continues to afflict HIV-1-infected individuals (Sacktor et al., 2016; Saylor et al., 2016). Up to 50% of the HIV-1-infected individuals exhibit some form of the HIV-1 associated neurocognitive disorders (HAND). Although cART can successfully control viremia, it has reduced effects on the expression of early viral gene products such as cytotoxic HIV-1 Tat protein that is lurking in tissues such as the CNS and lymph nodes, thereby contributing to neuroinflammation and HAND. In addition, drugs of abuse, such as opiates and cocaine, potentiate neuroinflammation associated with advanced HIV-1 infection. Several studies using the Simian immunodeficiency virus (SIV)-infected rhesus macaque model have been widely used to understand pathogenesis including the role of cytokines, chemokines and growth factors. In the SIV encephalitis monkey model, increased expression of PDGF-BB protein has been reported in the brain (Bethel-Brown et al., 2012). The authors also demonstrated HIV-1 Tat-mediated increased expression of PDGF-BB in astrocytes isolated from rat brains. In this study, PDGF-BB induction was regulated by activation of ERK1/2 and JNK signaling pathways and the downstream transcription factor early growth response gene, resulting ultimately in the release of chemokines and proinflammatory cytokines such as

monocyte chemoattractant protein-1 (MCP-1) and IL-1 $\beta$  as well as associated astrogliosis. In another report it was also shown that MCP-1, an important neuroinflammatory factor that is critical for the recruitment of monocytes in the CNS played a role in the pathogenesis of HAND, (Bethel-Brown et al., 2012). This study showed that exposure of monocytes to human recombinant PDGF-BB protein significantly increased the production and release of MCP-1 at both the RNA and protein levels, which in turn, was regulated by activation of ERK1/2, c-JNK and p38 MAPK and PI3K/Akt pathways and the downstream transcription factor, nuclear factor- $\kappa$ B (NF- $\kappa$ B). Furthermore, this study also showed that conditioned media from PDGF-BB-treated astrocytes increased monocyte transmigration through human brain microvascular endothelial cells, an effect that was blocked by STI-571, a tyrosine kinase inhibitor (PDGFR-blocker). These results thus indicated that activation of astrocytes by PDGF-BB resulted in exaggerated monocyte recruitment into the brain via MCP-1, thereby underscoring the role of astrocytes in HAND (Bethel-Brown et al., 2012). In another study, exposure of pericytes to HIV-1 Tat protein induced the expression and release of PDGF-BB, which in turn, via the autocrine loop led to increased loss of pericytes from the endothelial barrier via the activation of MAPK pathways resulting in increased neuroinflammation (Niu et al., 2014).

While the deleterious role of PDGF-BB in HIV-1 has been mentioned in the previous paragraph, paradoxically, its beneficial role has also been reported. It has been shown that PDGF-BB restores HIV-1 Tat -mediated impairment of neurogenesis via activating the GSK-3 $\beta$ / $\beta$ -catenin signaling axis (Chao et al., 2014). It has also been reported that pre-treatment of rat hippocampal neural progenitor cells with PDGF-BB restored proliferation that had been impaired by HIV-1 Tat via its cognate receptors. Further, this study identified an essential role of transient receptor potential canonical channels (TRPC 1) in PDGF-BB-mediated proliferation. Parallel but distinct ERK/CREB, PI3K/Akt signaling pathways with downstream activation of mTOR/4E-BP and p70S6K and NF- $\kappa$ B were critical for NPC proliferation. Together these data underpin the role of TRPC 1 channel as a novel target that regulates cell proliferation-mediated by PDGF-BB with implications for therapeutic intervention for reversal of impaired neurogenesis mediated by HIV-1 Tat (Yao et al., 2012). It was also demonstrated that human neuroblastoma cells, SH-SY5Y, exposed to HIV-1 Tat resulted in decreased expression of PDGF-CC, and that, pretreatment of SH-SY5Y cells with PDGF-CC abrogated HIV-1Tat-mediated neurotoxicity by mitigating apoptosis, neurite, and MAP-2 loss, via the PI3K/Akt signaling pathway (Peng et al., 2012). These findings collectively imply that PDGF-CC can be developed as a therapeutic target for HIV-1 Tat-mediated neurotoxicity.

Exposure of endothelial cells to cocaine was shown to increase endothelial barrier permeability, an effect that was also validated in cocaine-administered mice. This effect was shown to be abrogated in mice treated with PDGF-BB neutralizing antibody, thus underscoring the role of PDGF-BB as a vascular permeant (Yao et al., 2011a). Furthermore, it was also shown that cocaine-mediated induction of PDGF-BB in endothelial cells involved activation of Notch1 signaling (Yao et al., 2011b). In another study, PDGF-BB pretreatment of rat hippocampal neural progenitor cells restored HIV-1 Tat or cocaine-induced neuronal differentiation by mechanisms involving TRPC channels, ERK and Akt pathways (Yang et al., 2016).

Studies utilizing morphine-dependent SIV-infected rhesus macaques showed reduced expression of PDGF-BB with a concomitant increase in miR-29b in the basal ganglia compared with SIV-infected controls (Hu et al., 2012). This phenomenon was further validated in an *in vitro* system wherein exposure of astrocytes to HIV-1 Tat, and morphine resulted in increased release of exosomal

miR-29b. Subsequent addition of these astrocyte-derived exosomes to neuronal SH-SY5Y cells led to decreased expression of PDGF-BB (a known target of miR-29b), ultimately leading to neuronal apoptosis (Hu et al., 2012). Another study also reported increased apoptosis of human neurons following exposure to both HIV-1 Tat and morphine when compared with cells exposed to HIV-1 Tat

alone and that PDGF-BB reversed these effects (Malik et al., 2011). A recent study has demonstrated that morphine dysregulates synaptic balance in the hippocampus, a key center for learning and memory, via a novel signaling pathway involving reactive oxygen species, endoplasmic reticulum stress, and autophagy. Intriguingly, the detrimental effects of morphine on synaptic densities were

**Table 2**  
Pathological roles of PDGFs/PDGFRs in CNS diseases.

Disease	Isoforms involved	Regulation	Outcome	Model	References
Alzheimer disease	PDGF-AA	NA	Glial proliferation	Postmortem AD brain	Masliyah et al. (1995)
	PDGF-BB (Plasma)	Down	Correlated with mild cognitive impairment	AD patients	(Fraser, 1990)
	PDGF-BB (Neuron)	NA	Synaptic loss	Postmortem AD brain	(Masliyah et al., 1995)
	PDGF-B	Down	BBB disruption, Tau pathology, neuronal loss	AD transgenic mice	(Sagare et al., 2013; Winkler et al., 2014)
Parkinson disease	PDGF-AA (Plasma)	Up	Correlated with $\alpha$ -synuclein	PD patients	(Lue et al., 2016)
	PDGF-BB	NA	Intracerebroventricular administration of PDGF-BB restored striatal dopamine transporter binding sites leading to reversal of behavioral impairment	6- hydroxydopamine medial forebrain bundle lesion mouse model	(Zachrisson et al., 2011)
	PDGF-BB	NA	Intracerebroventricular administration of PDGF-BB increased dopamine transporter binding in the putamen	PD patients Phase 1 clinical trial	(Paul et al., 2015)
Amyotrophic Lateral Sclerosis	PDGF-BB (CSF)	Up	NA	ALS patients	(Furukawa et al., 2015)
	PDGF-CC (motor neurons)	Up	Disruption of blood-spinal cord barrier	SOD1 (G93A) mice	(Lewandowski et al., 2016b)
Cerebral ischemia	PDGF-BB (brain endothelial cells)	Up	Increased the expression of nerve growth factor and neurotrophin-3	Rat middle cerebral artery occlusion model	(Arimura et al., 2012)
	PDGF-B	NA	Cell growth and anti -apoptotic responses	Cultured pericytes	(Arimura et al., 2012)
	PDGF-CC	NA	PDGF CC treatment of cells under ischemic condition mobilized endothelial progenitor cells, induced differentiation of bone marrow cells into endothelial cells; and stimulated migration of endothelial cells	Endothelial and progenitor cells	(Li et al., 2005)
Glioblastoma	PDGFR- $\alpha$ , PDGF-AA, PDGF-BB	Up	Tumorigenesis	U87 human GBM cells	(Costa et al., 2012)
	PDGF-BB	Up	Downregulates miR-21 & miR-128 expression leading to increased cell proliferation	U87 human GBM cells and F98 rat glioma cells	(Costa et al., 2012)
	PDGF-CC	Up	Autocrine glioma signaling, glioma vessel maturation and stabilization	U87 human glioma cells	(di Tomaso et al., 2009)
	PDGF-CC	Up	Activation of survival and mitogenic pathways in glioblastomas	Brain tumor cell lines, brain tumor samples	(Lokker et al., 2002)
HIV-1	PDGF-DD	Up	Secretion of MCP-1 and IL-1 $\beta$ , and astrogliosis.	Astrocytes from rat brain	(Bethel-Brown et al., 2012)
	PDGF-BB	Up	Loss of pericytes from the endothelial barrier and neuroinflammation	Pericytes	(Niu et al., 2015; Niu et al., 2014)
	PDGF-BB	Up	Restored HIV-1 Tat -mediated impairment of neurogenesis	Neuronal precursor cells	(Chao et al., 2014)
HIV-1 and drugs of abuse	PDGF-BB	NA	Restored HIV-1 Tat & cocaine-mediated impairment of neurogenesis via TRPC channels	Rat hippocampal neural progenitor cells	(Yao et al., 2012)
	PDGF-CC	Down	Neuroprotection against HIV-1 Tat involves TRPC-mediated inactivation of GSK 3 $\beta$	Human neuroblastoma SH-SY5Y cells	(Peng et al., 2012)
	PDGF-BB	Up	Cocaine-mediated induction of PDGF-BB	Human brain microvascular endothelial cells	(Yao et al., 2011b)
	PDGF-BB	NA	Restored HIV-1 Tat/cocaine-induced neuronal differentiation via TRPC, ERK & Akt pathway	Rat hippocampal neural progenitor cells	(Yang et al., 2016)
	PDGF-BB	Down	Involved upregulation of miR-29b in the basal ganglia of morphine dependent SIV-infected rhesus macaques	Basal ganglia SIV-infected rhesus macaques	(Hu et al., 2012)
	PDGF-BB	Down	Exposure of astrocytes to HIV-1 Tat & morphine resulted in induction of exosomal miR-29b that was taken up by neurons leading to apoptosis.	Astrocytes and neuroblastoma cells	(Hu et al., 2012)
	PDGF-BB	NA	Restored HIV-1 Tat/cocaine-induced neuronal differentiation via TRPC, ERK & Akt pathway	Human neurons	(Malik et al., 2011)
	PDGF-BB	NA	Reversal of morphine-mediated synaptic alterations	Rat hippocampal neurons	(Cai et al., 2016)
	PDGF-BB	Up	Morphine mediated BBB impairment and morphine-induced tolerance	Human brain microvascular endothelial cells	(Wen et al., 2011)
	PDGFR- $\beta$	NA	Morphine tolerance	NA	(Wang et al., 2012)



shown to be reversed by PDGF-BB, suggesting its beneficial role. These results identified a novel cellular mechanism involved in morphine-mediated synaptic alterations with implications for therapeutic interventions by PDGF-BB (Cai et al., 2016).

Paradoxically, some studies have shown that exposure of endothelial cells to morphine resulted in upregulation of PDGF-BB expression, leading, in turn, to impairment of BBB and morphine-induced tolerance. In an *in vitro* model of endothelial cells, the functional significance of increased PDGF-BB expression following morphine exposure manifested as an increased breach of the endothelial barrier as evidenced by decreased expression of the tight junction protein, ZO-1 (Wen et al., 2011). In another study, it was observed that inhibiting PDGFR- $\beta$  signaling selectively eliminated morphine analgesic tolerance without altering acute analgesic effects of morphine in rats. Furthermore, morphine-induced PDGFR- $\beta$  signaling was necessary and sufficient for the behavioral expression of morphine tolerance (Wang et al., 2012). In summary, then, the beneficial or the detrimental effects of PDGF-PDGFR signaling discussed above depend on the cell type and the intrinsic host factors leading to various outcomes. Understanding the regulation of PDGF/PDGFR expression could thus provide insights into the development of potential therapeutic targets for intervention of morphine/cocaine-mediated toxicity (see Table 2).

## 10. Conclusions and future perspectives

This review describes the role of PDGFs-PDGFRs signaling in various CNS cell types such as the neurons, microglia, astrocytes, oligodendrocytes, and peripheral cells. PDGF-mediated signaling regulates diverse functions in the CNS such as neurogenesis, cell survival, synaptogenesis, modulation of ligand-gated ion channels, and development of specific types of neurons. In addition, this review summarizes the role of PDGFs/PDGFRs in several neurodegenerative diseases such as AD, PD, ALS, glioblastoma, cerebral ischemia, HIV-1 and drug abuse. Of importance is that the PDGF/PDGFR dyad can elicit paradoxical roles in the CNS, depending on the cell type and the activation stimuli. For example, in the endothelial cells, PDGF induction can lead to a breach of BBB with concomitant neuroinflammation. On the other hand, PDGF can provide trophic support for the neurons against a variety of neurotoxic mediators including cellular and viral products. Thus, depending on the cell type within the tissue, the same host factor can manifest diverse activation responses leading to several outcomes. The ultimate consequence of CNS diseases is thus a result of the ensuing shift in the balance between the neurotrophic versus neurotoxic products manifested overtime following activating stimuli or insults. Since this sort of paradoxical regulation is a common theme of cytokines and growth factors, caution must be exercised in development of therapeutic targets involving these mediators. Additionally, the pleiotropic functions of PDGFs make specific targeting of this pathway a major challenge possibly owing to a multiplicity of off-target effects. Although clinical trials for delivery of growth factors such as glial cell-derived neurotrophic factor and PDGF-BB, in the CNS have been initiated, outcomes remain limited. The reported PDGF-BB trial showed positive effects, further clinical trials are required. Future research targeting individual PDGFs including the less studied PDGF-CC and DD are warranted. Approaches for specific targeting and drug delivery in the CNS also need further investigation. Future development of specific nanoparticles for controlled delivery of PDGF or its mimetics, with the goal of targeting PDGFR in the diseased tissues/specific cells in conjunction with stem cell-based replacement therapies, could be the next frontier for treatment of neurodegenerative diseases. Such novel therapies would pave the way for the future development of therapeutic strategies for combating CNS pathologies.

## Acknowledgement

This work was supported by NIH grants: MH106425, DA035203, DA033150, DA027729.

## References

- Abbott, N.J., Patabendige, A.A., Dolman, D.E., Yusof, S.R., Begley, D.J., 2010. Structure and function of the blood-brain barrier. *Neurobiol. Dis.* 37 (1), 13–25.
- Alexander, G.E., 2004. Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder. *Dialogues Clin. Neurosci.* 6 (3), 259–280.
- Andrae, J., Gallini, R., Betsholtz, C., 2008. Role of platelet-derived growth factors in physiology and medicine. *Genes Dev.* 22 (10), 1276–1312.
- Andrae, J., Gouveia, L., Gallini, R., He, L., Fredriksson, L., Nilsson, I., Johansson, B.R., Eriksson, U., Betsholtz, C., 2016. A role for PDGF-C/PDGFR $\alpha$  signaling in the formation of the meningeal basement membranes surrounding the cerebral cortex. *Biol. Open.* 5 (4), 461–474.
- Arimura, K., Ago, T., Kamouchi, M., Nakamura, K., Ishitsuka, K., Kuroda, J., Sugimori, H., Ooboshi, H., Sasaki, T., Kitazono, T., 2012. PDGF receptor beta signaling in pericytes following ischemic brain injury. *Curr. Neurovasc. Res.* 9 (1), 1–9.
- Armulik, A., Genove, G., Mae, M., Nisancioglu, M.H., Wallgard, E., Niaudet, C., He, L., Norlin, J., Lindblom, P., Strittmatter, K., Johansson, B.R., Betsholtz, C., 2010. Pericytes regulate the blood-brain barrier. *Nature* 468 (7323), 557–561.
- Auestad, N., Korsak, R.A., Morrow, J.W., Edmond, J., 1991. Fatty acid oxidation and ketogenesis by astrocytes in primary culture. *J. Neurochem.* 56 (4), 1376–1386.
- Baloyannis, S.J., Baloyannis, I.S., 2012. The vascular factor in Alzheimer's disease: a study in Golgi technique and electron microscopy. *J. Neurol. Sci.* 322 (1–2), 117–121.
- Beazely, M.A., Lim, A., Li, H., Trepanier, C., Chen, X., Sidhu, B., Macdonald, J.F., 2009. Platelet-derived growth factor selectively inhibits NR2B-containing N-methyl-D-aspartate receptors in CA1 hippocampal neurons. *J. Biol. Chem.* 284 (12), 8054–8063.
- Bethel-Brown, C., Yao, H., Hu, G., Buch, S., 2012. Platelet-derived growth factor (PDGF)-BB-mediated induction of monocyte chemoattractant protein 1 in human astrocytes: implications for HIV-associated neuroinflammation. *J. Neuroinflammation* 9, 262.
- Betsholtz, C., 2004. Insight into the physiological functions of PDGF through genetic studies in mice. *Cytokine Growth Factor Rev.* 15 (4), 215–228.
- Bjorkqvist, M., Ohlsson, M., Minthon, L., Hansson, O., 2012. Evaluation of a previously suggested plasma biomarker panel to identify Alzheimer's disease. *PLoS One* 7 (1), e29868.
- Bostrom, H., Gritli-Linde, A., Betsholtz, C., 2002. PDGF-A/PDGFR  $\alpha$ -receptor signaling is required for lung growth and the formation of alveoli but not for early lung branching morphogenesis. *Dev. Dyn.* 223 (1), 155–162.
- Cabezas, R., Avila-Rodriguez, M., Vega-Vela, N.E., Echeverria, V., Gonzalez, J., Hidalgo, O.A., Santos, A.B., Aliev, G., Barreto, G.E., 2016. Growth factors and astrocytes metabolism: possible roles for platelet derived growth factor. *Med. Chem.* 12 (3), 204–210.
- Cai, Y., Yang, L., Hu, G., Chen, X., Niu, F., Yuan, L., Liu, H., Xiong, H., Arikath, J., Buch, S., 2016. Regulation of morphine-induced synaptic alterations: role of oxidative stress, ER stress, and autophagy. *J. Cell Biol.* 215 (2), 245–258.
- Chao, J., Yang, L., Yao, H., Buch, S., 2014. Platelet-derived growth factor-BB restores HIV Tat-mediated impairment of neurogenesis: role of GSK-3 $\beta$ /catenin. *J. Neuroimmune Pharmacol.* 9 (2), 259–268.
- Chen, P.H., Chen, X., He, X., 2013a. Platelet-derived growth factors and their receptors: structural and functional perspectives. *Biochim. Biophys. Acta.* 1834 (10), 2176–2186.
- Chen, S., Sayana, P., Zhang, X., Le, W., 2013b. Genetics of amyotrophic lateral sclerosis: an update. *Mol. Neurodegener.* 8, 28.
- Chen, Y.Y., Liu, X.W., Gong, T.X., Zhang, Z.Y., Liu, Y.E., Zhang, Y.B., Xiang, L.B., Xia, H., 2014. Role of platelet derived growth factor (PDGF) in reverting neuronal nuclear and soma size alterations in NSC-34 cells exposed to cerebrospinal fluid from amyotrophic lateral sclerosis patients. *Clin. Neurol. Neurosurg.* 120, 1–5.
- Cheng, B., Mattson, M.P., 1995. PDGFs protect hippocampal neurons against energy deprivation and oxidative injury: evidence for induction of antioxidant pathways. *J. Neurosci.* 15 (11), 7095–7104.
- Chih, C.P., Roberts Jr., E.L., 2003. Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis. *J. Cereb. Blood Flow Metab.* 23 (11), 1263–1281.
- Chojnacki, A., Kelly, J.J., Hader, W., Weiss, S., 2008. Distinctions between fetal and adult human platelet-derived growth factor-responsive neural precursors. *Ann. Neurol.* 64 (2), 127–142.
- Chojnacki, A., Weiss, S., 2004. Isolation of a novel platelet-derived growth factor-responsive precursor from the embryonic ventral forebrain. *J. Neurosci.* 24 (48), 10888–10899.
- Clara, C.A., Marie, S.K., de Almeida, J.R., Wakamatsu, A., Oba-Shinjo, S.M., Uno, M., Neville, M., Rosenberg, S., 2014. Angiogenesis and expression of PDGF-C, VEGF, CD105 and HIF-1 $\alpha$  in human glioblastoma. *Neuropathology* 34 (4), 343–352.
- Clarke, L.E., Barres, B.A., 2013. Emerging roles of astrocytes in neural circuit development. *Nat. Rev. Neurosci.* 14 (5), 311–321.

- Colombo, E., Farina, C., 2016. Astrocytes: key regulators of neuroinflammation. *Trends Immunol.* 37 (9), 608–620.
- Costa, P.M., Cardoso, A.L., Pereira de Almeida, L.F., Bruce, J.N., Canoll, P., Pedrosa de Lima, M.C., 2012. PDGF-B-mediated downregulation of miR-21: new insights into PDGF signaling in glioblastoma. *Hum. Mol. Genet.* 21 (23), 5118–5130.
- Dai, C., Celestino, J.C., Okada, Y., Louis, D.N., Fuller, G.N., Holland, E.C., 2001. PDGF autocrine stimulation dedifferentiates cultured astrocytes and induces oligodendrogliomas and oligoastrocytomas from neural progenitors and astrocytes in vivo. *Genes Dev.* 15 (15), 1913–1925.
- di Tomaso, E., London, N., Fuja, D., Logie, J., Tyrrell, J.A., Kamoun, W., Munn, L.L., Jain, R.K., 2009. PDGF-C induces maturation of blood vessels in a model of glioblastoma and attenuates the response to anti-VEGF treatment. *PLoS One* 4 (4), e5123.
- Ding, H., Wu, X., Bostrom, H., Kim, I., Wong, N., Tsoi, B., O'Rourke, M., Koh, G.Y., Soriano, P., Betsholtz, C., Hart, T.C., Marazita, M.L., Field, L.L., Tam, P.P., Nagy, A., 2004. A specific requirement for PDGF-C in palate formation and PDGFR- $\alpha$  signaling. *Nat. Genet.* 36 (10), 1111–1116.
- Egawa-Tsuzuki, T., Ohno, M., Tanaka, N., Takeuchi, Y., Uramoto, H., Faigle, R., Funa, K., Ishii, Y., Sasahara, M., 2004. The PDGF B-chain is involved in the ontogenic susceptibility of the developing rat brain to NMDA toxicity. *Exp. Neurol.* 186 (1), 89–98.
- Erlandsson, A., Enarsson, M., Forsberg-Nilsson, K., 2001. Immature neurons from CNS stem cells proliferate in response to platelet-derived growth factor. *J. Neurosci.* 21 (10), 3483–3491.
- Farkas, E., Luiten, P.G., 2001. Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog. Neurobiol.* 64 (6), 575–611.
- Fernandovalenzuela, C., Kazlauskas, A., Weiner, J., 1997. Roles of platelet-derived growth factor in the developing and mature nervous systems. *Brain Res. Rev.* 24 (1), 77–89.
- Fraser, C.G., 1990. Analytical goals for haematology tests. *Eur. J. Haematol. Suppl.* 53, 2–5.
- Fredriksson, L., Nilsson, I., Su, E.J., Andrae, J., Ding, H., Betsholtz, C., Eriksson, U., Lawrence, D.A., 2012. Platelet-derived growth factor C deficiency in C57BL/6 mice leads to abnormal cerebral vascularization, loss of neuroepithelial integrity, and ventricular abnormalities. *Am. J. Pathol.* 180 (3), 1136–1144.
- Fruttiger, M., Calver, A.R., Kruger, W.H., Mudhar, H.S., Michalovich, D., Takakura, N., Nishikawa, S., Richardson, W.D., 1996. PDGF mediates a neuron-astrocyte interaction in the developing retina. *Neuron* 17 (6), 1117–1131.
- Fruttiger, M., Karlsson, L., Hall, A.C., Abramsson, A., Calver, A.R., Bostrom, H., Willetts, K., Bertold, C.H., Heath, J.K., Betsholtz, C., Richardson, W.D., 1999. Defective oligodendrocyte development and severe hypomyelination in PDGF-A knockout mice. *Development* 126 (3), 457–467.
- Funa, K., Sasahara, M., 2014. The roles of PDGF in development and during neurogenesis in the normal and diseased nervous system. *J. Neuroimmune. Pharmacol.* 9 (2), 168–181.
- Furukawa, T., Matsui, N., Fujita, K., Nodera, H., Shimizu, F., Miyamoto, K., Takahashi, Y., Kanda, T., Kusunoki, S., Izumi, Y., Kaji, R., 2015. CSF cytokine profile distinguishes multifocal motor neuropathy from progressive muscular atrophy. *Neurol. Neuroimmunol. Neuroinflamm.* 2 (5), e138.
- Gianni, D., Zambrano, N., Bimonte, M., Minopoli, G., Mercken, L., Talamo, F., Scaloni, A., Russo, T., 2003. Platelet-derived growth factor induces the beta-gamma-secretase-mediated cleavage of Alzheimer's amyloid precursor protein through a Src-Rac-dependent pathway. *J. Biol. Chem.* 278 (11), 9290–9297.
- Gliemann, J., Hermey, G., Nykjaer, A., Petersen, C.M., Jacobsen, C., Andreasen, P.A., 2004. The mosaic receptor sorLA/LR11 binds components of the plasminogen-activating system and platelet-derived growth factor-BB similarly to LRP1 (low-density lipoprotein receptor-related protein), but mediates slow internalization of bound ligand. *Biochem. J.* 381 (Pt 1), 203–212.
- Guha, A., Dasher, K., Black, P.M., Wagner, J.A., Stiles, C.D., 1995. Expression of PDGF and PDGF receptors in human astrocytoma operation specimens supports the existence of an autocrine loop. *Int. J. Cancer* 60 (2), 168–173.
- Halliday, M.R., Rege, S.V., Ma, Q., Zhao, Z., Miller, C.A., Winkler, E.A., Zlokovic, B.V., 2016. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J. Cereb. Blood. Flow. Metab.* 36 (1), 216–227.
- Hansson, E., Ronnback, L., 1995. Astrocytes in glutamate neurotransmission. *FASEB J.* 9 (5), 343–350.
- He, C., Zhao, C., Kumar, A., Lee, C., Chen, M., Huang, L., Wang, J., Ren, X., Jiang, Y., Chen, W., Wang, B., Gao, Z., Zhong, Z., Huang, Z., Zhang, F., Huang, B., Ding, H., Ju, R., Tang, Z., Liu, Y., Cao, Y., Li, X., Liu, X., 2014. Vasoprotective effect of PDGF-CC mediated by HMOX1 rescues retinal degeneration. *Proc. Natl. Acad. Sci. U. S. A.* 111 (41), 14806–14811.
- He, L., Lu, Q.R., 2013. Coordinated control of oligodendrocyte development by extrinsic and intrinsic signaling cues. *Neurosci. Bull.* 29 (2), 129–143.
- Heldin, C.H., Westermark, B., 1999. Mechanism of action and in vivo role of platelet-derived growth factor. *Physiol. Rev.* 79 (4), 1283–1316.
- Hellstrom, M., Kalen, M., Lindahl, P., Abramsson, A., Betsholtz, C., 1999. Role of PDGF-B and PDGFR-beta in recruitment of vascular smooth muscle cells and pericytes during embryonic blood vessel formation in the mouse. *Development* 126 (14), 3047–3055.
- Hermanson, M., Funa, K., Hartman, M., Claesson-Welsh, L., Heldin, C.H., Westermark, B., Nister, M., 1992. Platelet-derived growth factor and its receptors in human glioma tissue: expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops. *Cancer Res.* 52 (11), 3213–3219.
- Hermey, G., Sjogaard, S.S., Petersen, C.M., Nykjaer, A., Gliemann, J., 2006. Tumour necrosis factor alpha-converting enzyme mediates ectodomain shedding of Vps10p-domain receptor family members. *Biochem. J.* 395 (2), 285–293.
- Hou, X., Kumar, A., Lee, C., Wang, B., Arjunan, P., Dong, L., Maminishkis, A., Tang, Z., Li, Y., Zhang, F., Zhang, S.Z., Wardega, P., Chakrabarty, S., Liu, B., Wu, Z., Colosi, P., Fariss, R.N., Lennartsson, J., Nussenblatt, R., Gutkind, J.S., Cao, Y., Li, X., 2010. PDGF-CC blockade inhibits pathological angiogenesis by acting on multiple cellular and molecular targets. *Proc. Natl. Acad. Sci. U. S. A.* 107 (27), 12216–12221.
- Hu, G., Yao, H., Chaudhuri, A.D., Duan, M., Yelamanchili, S.V., Wen, H., Cheney, P.D., Fox, H.S., Buch, S., 2012. Exosome-mediated shuttling of microRNA-29 regulates HIV Tat and morphine-mediated neuronal dysfunction. *Cell Death Dis.* 3, e381.
- Huang, Y., Hoffman, C., Rajappa, P., Kim, J.H., Hu, W., Huse, J., Tang, Z., Li, X., Weksler, B., Bromberg, J., Lyden, D.C., Greenfield, J.P., 2014. Oligodendrocyte progenitor cells promote neovascularization in glioma by disrupting the blood-brain barrier. *Cancer Res.* 74 (4), 1011–1021.
- Huberman, M., Shalit, F., Roth-Deri, I., Gutman, B., Brodie, C., Kott, E., Sredni, B., 1994. Correlation of cytokine secretion by mononuclear cells of Alzheimer patients and their disease stage. *J. Neuroimmunol.* 52 (2), 147–152.
- Hurst Jr, N.J., Najy, A.J., Ustach, C.V., Movilla, L., Kim, H.R., 2012. Platelet-derived growth factor-C (PDGF-C) activation by serine proteases: implications for breast cancer progression. *Biochem. J.* 441 (3), 909–918.
- Ishii, Y., Oya, T., Zheng, L., Gao, Z., Kawaguchi, M., Sabit, H., Matsushima, T., Tokunaga, A., Ishizawa, S., Hori, E., Nabeshima, Y., Sasaoka, T., Fujimori, T., Mori, H., Sasahara, M., 2006. Mouse brains deficient in neuronal PDGF receptor-beta develop normally but are vulnerable to injury. *J. Neurochem.* 98 (2), 588–600.
- Itoh, Y., Toriumi, H., Yamada, S., Hoshino, H., Suzuki, N., 2011. Astrocytes and pericytes cooperatively maintain a capillary-like structure composed of endothelial cells on gel matrix. *Brain Res.* 1406, 74–83.
- Jackson, E.L., Garcia-Verdugo, J.M., Gil-Perotin, S., Roy, M., Quinones-Hinojosa, A., VandenBerg, S., Alvarez-Buylla, A., 2006. PDGFR  $\alpha$ -positive B cells are neural stem cells in the adult SVZ that form glioma-like growths in response to increased PDGF signaling. *Neuron* 51 (2), 187–199.
- Jellinger, K.A., Bancher, C., 1996. AD neuropathology. *Neurology* 46 (4), 1186–1187.
- Jin, K., Galvan, V., Xie, L., Mao, X.O., Gorostiza, O.F., Bredesen, D.E., Greenberg, D.A., 2004. Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPs-wld) mice. *Proc. Natl. Acad. Sci. U. S. A.* 101 (36), 13363–13367.
- Kazlauskas, A., 2017. PDGFs and their receptors. *Gene* 614, 1–7.
- Kirchhoff, F., Dringen, R., Giaume, C., 2001. Pathways of neuron-astrocyte interactions and their possible role in neuroprotection. *Eur. Arch. Psychiatry Clin. Neurosci.* 251 (4), 159–169.
- Kofuji, P., Newman, E.A., 2004. Potassium buffering in the central nervous system. *Neuroscience* 129 (4), 1045–1056.
- Krupinski, J., Issa, R., Bujny, T., Slevin, M., Kumar, P., Kumar, S., Kaluza, J., 1997. A putative role for platelet-derived growth factor in angiogenesis and neuroprotection after ischemic stroke in humans. *Stroke* 28 (3), 564–573.
- Lee, C., Zhang, F., Tang, Z., Liu, Y., Li, X., 2013. PDGF-C: a new performer in the neurovascular interplay. *Trends Mol. Med.* 19 (8), 474–486.
- Leveen, P., Pekny, M., Gebre-Medhin, S., Swolin, B., Larsson, E., Betsholtz, C., 1994. Mice deficient for PDGF B show renal, cardiovascular, and hematological abnormalities. *Genes Dev.* 8 (16), 1875–1887.
- Lewandowski, S.A., Fredriksson, L., Lawrence, D.A., Eriksson, U., 2016a. Pharmacological targeting of the PDGF-CC signaling pathway for blood-brain barrier restoration in neurological disorders. *Pharmacol. Ther.* 167, 108–119.
- Lewandowski, S.A., Nilsson, I., Fredriksson, L., Lonnnerberg, P., Muhl, L., Zeitelhofer, M., Adzemovic, M.Z., Nichterwitz, S., Lawrence, D.A., Hedlund, E., Eriksson, U., 2016b. Presymptomatic activation of the PDGF-CC pathway accelerates onset of ALS neurodegeneration. *Acta Neuropathol.* 131 (3), 453–464.
- Li, X., Tjwa, M., Moons, L., Fons, P., Noel, A., Ny, A., Zhou, J.M., Lennartsson, J., Li, H., Luttun, A., Ponten, A., Devy, L., Bouche, A., Oh, H., Manderveld, A., Blacher, S., Communi, D., Savi, P., Bono, F., Dowerchin, M., Foidart, J.M., Autiero, M., Herbert, J.M., Collen, D., Heldin, C.H., Eriksson, U., Carmeliet, P., 2005. Revascularization of ischemic tissues by PDGF-CC via effects on endothelial cells and their progenitors. *J. Clin. Invest.* 115 (1), 118–127.
- Lindahl, P., Johansson, B.R., Leveen, P., Betsholtz, C., 1997. Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. *Science* 277 (5323), 242–245.
- Liu, B., Teschemacher, A.G., Kasparov, S., 2017. Astroglia as a cellular target for neuroprotection and treatment of neuro-psychiatric disorders. *Glia* 65 (8), 1205–1226.
- Liu, Y., Fan, Z., Zhou, Y., Liu, M., Ding, F., Gu, X., 2009. The molecular cloning of platelet-derived growth factor-C (PDGF-C) gene of *Gekko japonicus* and its expression change in the spinal cord after tail amputation. *Cell. Mol. Neurobiol.* 29 (2), 263–271.
- Lokker, N.A., Sullivan, C.M., Hollenbach, S.J., Israel, M.A., Giese, N.A., 2002. Platelet-derived growth factor (PDGF) autocrine signaling regulates survival and mitogenic pathways in glioblastoma cells: evidence that the novel PDGF-C and PDGF-D ligands may play a role in the development of brain tumors. *Cancer Res.* 62 (13), 3729–3735.
- Lue, L.F., Schmitz, C.T., Snyder, N.L., Chen, K., Walker, D.G., Davis, K.J., Belden, C., Caviness, J.N., Driver-Dunckley, E., Adler, C.H., Sabbagh, M.N., Shill, H.A., 2016. Converging mediators from immune and trophic pathways to identify Parkinson disease dementia. *Neurol. Neuroimmunol. Neuroinflamm.* 3 (1), e193.
- Lutton, C., Young, Y.W., Williams, R., Meedeniya, A.C., Mackay-Sim, A., Goss, B., 2012. Combined VEGF and PDGF treatment reduces secondary degeneration after

- spinal cord injury. *J. Neurotrauma* 29 (5), 957–970.
- Ma, Q., Huang, B., Khatibi, N., Rolland 2nd, W., Suzuki, H., Zhang, J.H., Tang, J., 2011. PDGFR- $\alpha$  inhibition preserves blood-brain barrier after intracerebral hemorrhage. *Ann. Neurol.* 70 (6), 920–931.
- Malik, S., Khaliq, H., Buch, S., Seth, P., 2011. A growth factor attenuates HIV-1 Tat and morphine induced damage to human neurons: implication in HIV/AIDS-drug abuse cases. *PLoS One* 6 (3), e18116.
- Masliah, E., Mallory, M., Alford, M., Deteresa, R., Saitoh, T., 1995. PDGF is associated with neuronal and glial alterations of Alzheimer's disease. *Neurobiol. Aging* 16 (4), 549–556.
- Montagne, A., Barnes, S.R., Sweeney, M.D., Halliday, M.R., Sagare, A.P., Zhao, Z., Toga, A.W., Jacobs, R.E., Liu, C.Y., Amezcua, L., Harrington, M.G., Chui, H.C., Law, M., Zlokovic, B.V., 2015. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron* 85 (2), 296–302.
- Mudhar, H.S., Pollock, R.A., Wang, C., Stiles, C.D., Richardson, W.D., 1993. PDGF and its receptors in the developing rodent retina and optic nerve. *Development* 118 (2), 539–552.
- Murtie, J.C., Zhou, Y.X., Le, T.Q., Vana, A.C., Armstrong, R.C., 2005. PDGF and FGF2 pathways regulate distinct oligodendrocyte lineage responses in experimental demyelination with spontaneous remyelination. *Neurobiol. Dis.* 19 (1–2), 171–182.
- Nait Oumesmar, B., Vignais, L., Baron-Van Evercooren, A., 1997. Developmental expression of platelet-derived growth factor  $\alpha$ -receptor in neurons and glial cells of the mouse CNS. *J. Neurosci.* 17 (1), 125–139.
- Nicholas, R.S., Wing, M.G., Compston, A., 2001. Nonactivated microglia promote oligodendrocyte precursor survival and maturation through the transcription factor NF- $\kappa$ B. *Eur. J. Neurosci.* 13 (5), 959–967.
- Nikolakopoulou, A.M., Zhao, Z., Montagne, A., Zlokovic, B.V., 2017. Regional early and progressive loss of brain pericytes but not vascular smooth muscle cells in adult mice with disrupted platelet-derived growth factor receptor- $\beta$  signaling. *PLoS One* 12 (4), e0176225.
- Niu, F., Yao, H., Liao, K., Buch, S., 2015. HIV Tat 101-mediated loss of pericytes at the blood-brain barrier involves PDGF-BB. *Ther. Targets Neurol. Dis.* 2 (1).
- Niu, F., Yao, H., Zhang, W., Sutcliffe, R.L., Buch, S., 2014. Tat 101-mediated enhancement of brain pericyte migration involves platelet-derived growth factor subunit B homodimer: implications for human immunodeficiency virus-associated neurocognitive disorders. *J. Neurosci.* 34 (35), 11812–11825.
- Noraziti, A., Nguyen, M.N., Dickson, C.G., Tuxworth, G., Goss, B., Mackay-Sim, A., Meedeniya, A.C., 2011. Vascular endothelial growth factor and platelet derived growth factor modulates the glial response to a cortical stab injury. *Neuroscience* 192, 652–660.
- Padel, T., Ozen, I., Boix, J., Barbariga, M., Gaceb, A., Roth, M., Paul, G., 2016. Platelet-derived growth factor-BB has neurorestorative effects and modulates the pericyte response in a partial 6-hydroxydopamine lesion mouse model of Parkinson's disease. *Neurobiol. Dis.* 94, 95–105.
- Paul, G., Zachrisson, O., Varrone, A., Almqvist, P., Jerling, M., Lind, G., Rehnström, S., Linderöth, B., Bjartmarz, H., Shafer, L.L., Coffey, R., Svensson, M., Mercer, K.J., Forsberg, A., Hallidin, C., Svenningsson, P., Widner, H., Frisen, J., Palhagen, S., Haegerstrand, A., 2015. Safety and tolerability of intracerebroventricular PDGF-BB in Parkinson's disease patients. *J. Clin. Invest.* 125 (3), 1339–1346.
- Peng, F., Dhillon, N., Callen, S., Yao, H., Bokhari, S., Zhu, X., Baydoun, H.H., Buch, S., 2008. Platelet-derived growth factor protects neurons against gp120-mediated toxicity. *J. Neurovirol.* 14 (1), 62–72.
- Peng, F., Yao, H., Akturk, H.K., Buch, S., 2012. Platelet-derived growth factor CC-mediated neuroprotection against HIV Tat involves TRPC-mediated inactivation of GSK 3 $\beta$ . *PLoS One* 7 (10), e47572.
- Peng, F., Yao, H., Bai, X., Zhu, X., Reiner, B.C., Beazely, M., Funa, K., Xiong, H., Buch, S., 2010. Platelet-derived growth factor-mediated induction of the synaptic plasticity gene Arc/Arg3.1. *J. Biol. Chem.* 285 (28), 21615–21624.
- Pfeiffer, S.E., Warrington, A.E., Bansal, R., 1993. The oligodendrocyte and its many cellular processes. *Trends Cell Biol.* 3 (6), 191–197.
- Plemel, J.R., Chojnacki, A., Sparling, J.S., Liu, J., Plunet, W., Duncan, G.J., Park, S.E., Weiss, S., Tetzlaff, W., 2011. Platelet-derived growth factor-responsive neural precursors give rise to myelinating oligodendrocytes after transplantation into the spinal cords of contused rats and dysmyelinated mice. *Glia* 59 (12), 1891–1910.
- Raff, M.C., Lillien, L.E., Richardson, W.D., Burne, J.F., Noble, M.D., 1988. Platelet-derived growth factor from astrocytes drives the clock that times oligodendrocyte development in culture. *Nature* 333 (6173), 562–565.
- Ray, S., Britschgi, M., Herbert, C., Takeda-Uchimura, Y., Boxer, A., Blennow, K., Friedman, L.F., Galasko, D.R., Jutel, M., Karydas, A., Kaye, J.A., Leszek, J., Miller, B.L., Minthon, L., Quinn, J.F., Rabinovici, G.D., Robinson, W.H., Sabbagh, M.N., So, Y.T., Sparks, D.L., Tabaton, M., Tinklenberg, J., Yesavage, J.A., Tibshirani, R., Wyss-Coray, T., 2007. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat. Med.* 13 (11), 1359–1362.
- Renner, O., Tsimpas, A., Kostin, S., Valable, S., Petit, E., Schaper, W., Marti, H.H., 2003. Time- and cell type-specific induction of platelet-derived growth factor receptor- $\beta$  during cerebral ischemia. *Brain Res Mol Brain Res* 113 (1–2), 44–51.
- Richardson, W.D., Pringle, N., Mosley, M.J., Westermark, B., Dubois-Dalcq, M., 1988. A role for platelet-derived growth factor in normal gliogenesis in the central nervous system. *Cell* 53 (2), 309–319.
- Richarte, A.M., Mead, H.B., Tallquist, M.D., 2007. Cooperation between the PDGF receptors in cardiac neural crest cell migration. *Dev. Biol.* 306 (2), 785–796.
- Robberecht, W., Philips, T., 2013. The changing scene of amyotrophic lateral sclerosis. *Nat. Rev. Neurosci.* 14 (4), 248–264.
- Rodriguez-Gonzalez, R., Blanco, M., Rodriguez-Yanez, M., Moldes, O., Castillo, J., Sobrino, T., 2013. Platelet derived growth factor-CC isoform is associated with hemorrhagic transformation in ischemic stroke patients treated with tissue plasminogen activator. *Atherosclerosis* 226 (1), 165–171.
- Sacktor, N., Skolasky, R.L., Seaberg, E., Munro, C., Becker, J.T., Martin, E., Ragin, A., Levine, A., Miller, E., 2016. Prevalence of HIV-associated neurocognitive disorders in the multicenter AIDS cohort study. *Neurology* 86 (4), 334–340.
- Sagare, A.P., Bell, R.D., Zhao, Z., Ma, Q., Winkler, E.A., Ramanathan, A., Zlokovic, B.V., 2013. Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nat. Commun.* 4, 2932.
- Sagare, A.P., Sweeney, M.D., Makhanoff, J., Zlokovic, B.V., 2015. Shedding of soluble platelet-derived growth factor receptor- $\beta$  from human brain pericytes. *Neurosci. Lett.* 607, 97–101.
- Sakata, M., Yamamoto, H., Hashimoto, N., Iihara, K., Tsukahara, T., Taniguchi, T., Kikuchi, H., 1998. Induction of infarct tolerance by platelet-derived growth factor against reversible focal ischemia. *Brain Res.* 784 (1–2), 250–255.
- Sasahara, M., Sato, H., Iihara, K., Wang, J., Chue, C.H., Takayama, S., Hayase, Y., Hazama, F., 1995. Expression of platelet-derived growth factor B-chain in the mature rat brain and pituitary gland. *Brain Res Mol Brain Res* 32 (1), 63–74.
- Saylor, D., Dickens, A.M., Sacktor, N., Haughey, N., Slusher, B., Pletnikov, M., Mankowski, J.L., Brown, A., Volsky, D.J., McArthur, J.C., 2016. HIV-associated neurocognitive disorder—pathogenesis and prospects for treatment. *Nat. Rev. Neurol.* 12 (4), 234–248.
- Schatteman, G.C., Morrison-Graham, K., van Koppen, A., Weston, J.A., Bowen-Pope, D.F., 1992. Regulation and role of PDGF receptor  $\alpha$ -subunit expression during embryogenesis. *Development* 115 (1), 123–131.
- Sengillo, J.D., Winkler, E.A., Walker, C.T., Sullivan, J.S., Johnson, M., Zlokovic, B.V., 2013. Deficiency in mural vascular cells coincides with blood-brain barrier disruption in Alzheimer's disease. *Brain Pathol.* 23 (3), 303–310.
- Shamah, S.M., Stiles, C.D., Guha, A., 1993. Dominant-negative mutants of platelet-derived growth factor revert the transformed phenotype of human astrocytoma cells. *Mol. Cell Biol.* 13 (12), 7203–7212.
- Shen, J., Ishii, Y., Xu, G., Dang, T.C., Hamashima, T., Matsushima, T., Yamamoto, S., Hattori, Y., Takatsuru, Y., Nabekura, J., Sasahara, M., 2012. PDGFR- $\beta$  as a positive regulator of tissue repair in a mouse model of focal cerebral ischemia. *J. Cereb. Blood Flow Metab.* 32 (2), 353–367.
- Soriano, P., 1997. The PDGF  $\alpha$  receptor is required for neural crest cell development and for normal patterning of the somites. *Development* 124 (14), 2691–2700.
- Stefanitsch, C., Lawrence, A.L., Olverling, A., Nilsson, I., Fredriksson, L., 2015. tPA deficiency in mice leads to rearrangement in the cerebrovascular tree and cerebrovascular malformations. *Front. Cell. Neurosci.* 9, 456.
- Strawn, L.M., Mann, E., Elliger, S.S., Chu, L.M., Germain, L.L., Niederfellner, G., Ullrich, A., Shawver, L.K., 1994. Inhibition of glioma cell growth by a truncated platelet-derived growth factor- $\beta$  receptor. *J. Biol. Chem.* 269 (33), 21215–21222.
- Su, E.J., Cao, C., Fredriksson, L., Nilsson, I., Stefanitsch, C., Stevenson, T.K., Zhao, J., Ragsdale, M., Sun, Y.Y., Yepes, M., Kuan, C.Y., Eriksson, U., Strickland, D.K., Lawrence, D.A., Zhang, L., 2017. Microglial-mediated PDGF-CC activation increases cerebrovascular permeability during ischemic stroke. *Acta Neuropathol.* 134 (4), 585–604.
- Su, E.J., Fredriksson, L., Geyer, M., Folestad, E., Cale, J., Andrae, J., Gao, Y., Pietras, K., Mann, K., Yepes, M., Strickland, D.K., Betsholtz, C., Eriksson, U., Lawrence, D.A., 2008. Activation of PDGF-CC by tissue plasminogen activator impairs blood-brain barrier integrity during ischemic stroke. *Nat. Med.* 14 (7), 731–737.
- Su, E.J., Fredriksson, L., Kanzawa, M., Moore, S., Folestad, E., Stevenson, T.K., Nilsson, I., Sashindranath, M., Schielke, G.P., Warnock, M., Ragsdale, M., Mann, K., Lawrence, A.L., Medcalf, R.L., Eriksson, U., Murphy, G.G., Lawrence, D.A., 2015. Imatinib treatment reduces brain injury in a murine model of traumatic brain injury. *Front. Cell. Neurosci.* 9, 385.
- Sweeney, M.D., Ayyadurai, S., Zlokovic, B.V., 2016. Pericytes of the neurovascular unit: key functions and signaling pathways. *Nat. Neurosci.* 19 (6), 771–783.
- Tang, Z., Arjunan, P., Lee, C., Li, Y., Kumar, A., Hou, X., Wang, B., Vardega, P., Zhang, F., Dong, L., Zhang, Y., Zhang, S.Z., Ding, H., Fariss, R.N., Becker, K.G., Lennartsson, J., Nagai, N., Cao, Y., Li, X., 2010. Survival effect of PDGF-CC rescues neurons from apoptosis in both brain and retina by regulating GSK3 $\beta$  phosphorylation. *J. Exp. Med.* 207 (4), 867–880.
- Tsai, J.C., Goldman, C.K., Gillespie, G.Y., 1995. Vascular endothelial growth factor in human glioma cell lines: induced secretion by EGF, PDGF-BB, and bFGF. *J. Neurosurg.* 82 (5), 864–873.
- Tseng, H.C., Dichter, M.A., 2005. Platelet-derived growth factor-BB pretreatment attenuates excitotoxic death in cultured hippocampal neurons. *Neurobiol. Dis.* 19 (1–2), 77–83.
- Uhrbom, L., Hesselager, G., Nister, M., Westermark, B., 1998. Induction of brain tumors in mice using a recombinant platelet-derived growth factor B-chain retrovirus. *Cancer Res* 58 (23), 5275–5279.
- Valenzuela, C.F., Kazlauskas, A., Weiner, J.L., 1997. Roles of platelet-derived growth factor in the developing and mature nervous systems. *Brain Res Brain Res Rev* 24 (1), 77–89.
- Vasefi, M.S., Kruk, J.S., Heikkilä, J.J., Beazely, M.A., 2013. 5-Hydroxytryptamine type 7 receptor neuroprotection against NMDA-induced excitotoxicity is PDGF $\beta$  receptor dependent. *J. Neurochem.* 125 (1), 26–36.
- Vasefi, M.S., Kruk, J.S., Liu, H., Heikkilä, J.J., Beazely, M.A., 2012. Activation of 5-HT7



- receptors increases neuronal platelet-derived growth factor beta receptor expression. *Neurosci. Lett.* 511 (2), 65–69.
- Wang, Y., Abu-Asab, M.S., Yu, C.R., Tang, Z., Shen, D., Tuo, J., Li, X., Chan, C.C., 2014. Platelet-derived growth factor (PDGF)-C inhibits neuroretinal apoptosis in a murine model of focal retinal degeneration. *Lab. Invest.* 94 (6), 674–682.
- Wang, Y., Barker, K., Shi, S., Diaz, M., Mo, B., Gutstein, H.B., 2012. Blockade of PDGFR-beta activation eliminates morphine analgesic tolerance. *Nat. Med.* 18 (3), 385–387.
- Wen, H., Lu, Y., Yao, H., Buch, S., 2011. Morphine induces expression of platelet-derived growth factor in human brain microvascular endothelial cells: implication for vascular permeability. *PLoS One* 6 (6), e21707.
- Westermarck, B., 2014. Platelet-derived growth factor in glioblastoma-driver or biomarker? *Ups. J. Med. Sci.* 119 (4), 298–305.
- Williams, B.P., Park, J.K., Alberta, J.A., Muhlebach, S.G., Hwang, G.Y., Roberts, T.M., Stiles, C.D., 1997. A PDGF-regulated immediate early gene response initiates neuronal differentiation in ventricular zone progenitor cells. *Neuron* 18 (4), 553–562.
- Winkler, E.A., Sagare, A.P., Zlokovic, B.V., 2014. The pericyte: a forgotten cell type with important implications for Alzheimer's disease? *Brain Pathol.* 24 (4), 371–386.
- Yang, L., Chen, X., Hu, G., Cai, Y., Liao, K., Buch, S., 2016. Mechanisms of platelet-derived growth factor-BB in restoring HIV Tat-cocaine-mediated impairment of neuronal differentiation. *Mol. Neurobiol.* 53 (9), 6377–6387.
- Yao, H., Duan, M., Buch, S., 2011a. Cocaine-mediated induction of platelet-derived growth factor: implication for increased vascular permeability. *Blood* 117 (8), 2538–2547.
- Yao, H., Duan, M., Hu, G., Buch, S., 2011b. Platelet-derived growth factor B chain is a novel target gene of cocaine-mediated Notch1 signaling: implications for HIV-associated neurological disorders. *J. Neurosci.* 31 (35), 12449–12454.
- Yao, H., Duan, M., Yang, L., Buch, S., 2012. Platelet-derived growth factor-BB restores human immunodeficiency virus Tat-cocaine-mediated impairment of neurogenesis: role of TRPC1 channels. *J. Neurosci.* 32 (29), 9835–9847.
- Yin, K.J., Hamblin, M., Chen, Y.E., 2015. Angiogenesis-regulating microRNAs and ischemic stroke. *Curr. Vasc. Pharmacol.* 13 (3), 352–365.
- Yoshida, D., Kim, K., Noha, M., Teramoto, A., 2006. Hypoxia inducible factor 1-alpha regulates of platelet derived growth factor-B in human glioblastoma cells. *J. Neuro Oncol.* 76 (1), 13–21.
- Zachrisson, O., Zhao, M., Andersson, A., Dannaeus, K., Hagglad, J., Isacson, R., Nielsen, E., Patrone, C., Ronnholm, H., Wikstrom, L., Delfani, K., McCormack, A.L., Palmer, T., Di Monte, D.A., Hill, M.P., Janson Lang, A.M., Haegerstrand, A., 2011. Restorative effects of platelet derived growth factor-BB in rodent models of Parkinson's disease. *J. Parkinson's Dis.* 1 (1), 49–63.
- Zlokovic, B.V., Deane, R., Sagare, A.P., Bell, R.D., Winkler, E.A., 2010. Low-density lipoprotein receptor-related protein-1: a serial clearance homeostatic mechanism controlling Alzheimer's amyloid beta-peptide elimination from the brain. *J. Neurochem.* 115 (5), 1077–1089.