European Journal of Cell Biology 91 (2012) 542–551

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.de/ejcb

Review

The platelet-derived growth factor system in renal disease: An emerging role of endogenous inhibitors

Claudia R.C. van Roeyen*, Tammo Ostendorf, Jürgen Floege

Department of Nephrology and Clinical Immunology, RWTH University Hospital Aachen, Pauwelsstr. 30, D-52057 Aachen, Germany

ARTICLE INFO

Article history:
Received 16 May 2011
Received in revised form 5 July 2011
Accepted 5 July 2011

Keywords:
Growth factors
Renal disease
Inhibitors
Antagonist

ABSTRACT

The platelet-derived growth factor (PDGF) family consists of four isoforms which are secreted as homodimers (PDGF-AA, PDGF-BB, PDGF-CC and PDGF-DD) or heterodimers (PDGF-AB), and two receptor chains (PDGFR-α and -β). All members of the PDGF system are constitutively or inducibly expressed in renal cells and are involved in the regulation of cell proliferation and migration, the accumulation of extracellular matrix proteins and the secretion of pro- and anti-inflammatory mediators. Particular roles have been identified in mediating mesangioproliferative changes, renal interstitial fibrosis and glomerular angiogenesis. Different endogenous inhibitors of PDGF-induced biological responses exist which affect the activation/deactivation of PDGF isoforms, the activity of the PDGFRs, or which block downstream signaling pathways of the autophosphorylated PDGFRs. The novel endogenous inhibitor nephroblastoma overexpressed gene (NOV, CCN3) reduces PDGF-induced cell proliferation and is downregulated by PDGF isoforms itself. Among all identified inhibitors only few "true" PDGF antagonists have been identified. A better understanding of these inhibitors may aid in the design of novel therapeutic approaches to PDGF-mediated diseases.

Introduction

The platelet-derived growth factor (PDGF) family consists of four different isoforms: PDGF-A, -B, -C and -D (Fig. 1). While the two classical isoforms PDGF-A and -B are secreted as homo- or heterodimers, the new isoforms PDGF-C and -D form homodimers only (Floege et al., 2008). PDGF-C and -D are secreted as latent factors which need extracellular cleavage of the CUB domain by the tissue-type plasminogen activator (tPA, PDGF-C), the urokinase-type plasminogen activator (uPA, PDGF-D) or matriptase (PDGF-D) for receptor binding and activation (Bergsten et al., 2001; LaRochelle et al., 2001; Li et al., 2000; Reigstad et al., 2005; Ustach et al., 2010). PDGF-A and -B bind to the extracellular matrix via a c-terminal retention sequence, which can be proteolytically cleaved (Heldin and Westermark, 1999). PDGF-DD lacks the basic amino acid sequence that mediates binding of PDGF-BB to the extracellular matrix (Li and Eriksson, 2003).

PDGF receptors (PDGFR) are dimers which consist of two different receptor chains (PDGFR-α and -β) (Fig. 1). Whereas PDGF-B binds to both receptor chains, PDGF-A and -C are specific ligands for the PDGFR-α chain. PDGF-D binds predominantly to the homodimeric PDGFR-ββ and with lower affinity to the heterodimeric PDGFR-αβ (Floege et al., 2008; Reigstad et al., 2005).

In recent years, several experimental studies with e.g., PDGF infusion or specific antagonism have been identified especially PDGF-B, -C and -D as key factors in the development of renal pathology, which drive mesangial proliferative changes, renal fibrosis or glomerular angiogenesis (reviewed in (Floege et al., 2008; Ostendorf et al., 2011) and Fig. 2). Therefore, next to recently developed PDGF antagonists, the identification and manipulation of endogenous inhibitors of PDGF and its receptors could become a prospective alternative in terms of therapeutic approaches in many renal diseases.

PDGF distribution in normal and diseased kidney

The expression patterns of PDGF and PDGFR in healthy and diseased kidneys have recently been reviewed in detail (Floege et al., 2008; Ostendorf et al., 2011) and are summarized in Table 1. Briefly, in the adult healthy kidney, PDGF-A is expressed by mature podocytes, endothelial and smooth muscle cells of arteries and epithelial cells of the distal nephron including collecting ducts and the urothelium, whereas PDGF-B is expressed by arterial smooth muscle cells (Alpers et al., 1995; Ghanem et al., 2010; Seifert et al., 1998; Taneda et al., 2003b). The expression of the two novel PDGF isoforms seems to be species specific. In the human kidney, mesangial cells, arterial endothelial and smooth muscle cells, parietal

* Corresponding author. Tel.: +49 241 8089258; fax: +49 241 8082446.
E-mail address: cvanroeyen@ukaachen.de (C.R.C. van Roeyen).

0171-9335/$ – see front matter © 2011 Elsevier GmbH. All rights reserved.
doi:10.1016/j.ejcb.2011.07.003

Table 1
Expression of PDGF isoforms and receptors in the healthy adult kidney.

	Glomerulus				Arteries		Tubulus		Interstitium	
	Mesangial cells	Podocytes	Parietal epithelial cells	Endothelial cells	Smooth muscle cells	Endothelial cells	Distal tubular cells	Collecting duct cells	Interstitial cells	
PDGF-A	–	Human	–	–	Human mouse	Human	Human mouse	Human	–	(Alpers et al., 1995; Ghanem et al., 2010; Seifert et al., 1998; Taneda et al., 2003b)
PDGF-B	–	–	–	–	Mouse	–	–	–	–	(Alpers et al., 1995; Seifert et al., 1998; Taneda et al., 2003b)
PDGF-C	Human	–	Human	Mouse	Human rat mouse	Human mouse	Human	Human rat	–	(Eitner et al., 2002, 2003, 2008; Fang et al., 2004; Taneda et al., 2003b)
PDGF-D	Human rat mouse	Human	Human	–	Human rat mouse	–	Human	Human	–	(Changsirikulchai et al., 2002; Liu et al., 2008; Ostendorf et al., 2003; Taneda et al., 2003b)
PDGFR-α	Human mouse	–	–	–	Human	–	Human	Human	Human mouse	(Floege et al., 1997; Gesualdo et al., 1994; Ghanem et al., 2010; Matsumoto et al., 2002; Seifert et al., 1998; Taneda et al., 2003b)
PDGFR-β	Human mouse	–	Human	–	Human	–	–	–	Human mouse	(Alpers et al., 1993; Gesualdo et al., 1994; Liu et al., 2008; Seifert et al., 1998; Taneda et al., 2003b)

Abbreviations: PDGF, platelet-derived growth factor; PDGFR, PDGF-receptor; –, not expressed.