Platelet-derived growth factors (PDGFs) in glomerular and tubulointerstitial fibrosis

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Renal fibrosis is the hallmark of chronic kidney disease progression and is characterized by an exaggerated wound-healing process with the production of renal scar tissue. It comprises both the glomerular and the tubulointerstitial compartments. Among the factors that contribute to kidney fibrosis, the members of the platelet-derived growth factor (PDGF) family are among the best characterized ones. They appear to be the key factors in driving renal fibrosis, independent of the underlying kidney disease. The PDGF family consists of four isoforms (PDGF-A, -B, -C, and -D) and two receptor chains (PDGFR-α and -β), which are constitutively or inducibly expressed in most renal cells. These components have an irreplaceable role in kidney development by recruitment of mesenchymal cells to the glomerular and tubulointerstitial compartments. They further regulate multiple pathophysiologic processes including cell proliferation, cell migration, expression and accumulation of extracellular matrix, production and secretion of pro- and anti-inflammatory mediators, vascular permeability, and hemodynamics. This review provides a brief update on the role of different PDGF isoforms in the development of glomerulosclerosis and tubulointerstitial fibrosis, newly identified endogeneous PDGF antagonists, and resulting potential therapies.

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Nearly all progressive renal diseases funnel into renal fibrosis as a final common pathway and subsequently lead to end-stage renal disease. Apart from the medical consequences, this is accompanied by an immense economic and social burden. Fibrotic kidneys are characterized by glomerulosclerosis, tubular atrophy and dilatation, tubulointerstitial fibrosis, and rarefaction of glomerular as well as peritubular capillaries.[1] Similarities between the fibrogenic mechanisms, independent of the underlying disease and by involving nearly all renal cells, make these processes an attractive therapeutic target to halt or even induce regression of renal fibrosis. Meanwhile, a huge number of molecules with pro- or antifibrotic properties in the kidney have been identified.[2] In numerous studies performed during the last 15–20 years, it has been established that platelet-derived growth factors (PDGFs) have a crucial role in driving these processes that ultimate lead to fibrosis, especially in the kidney but also in other organs.[3] Moreover, PDGFs and their receptors have been demonstrated to be important in embryonic development, angiogenesis, and hematopoiesis.[4] They have also been implicated in many other diseases, such as autocrine and paracrine PDGF signaling in cancer.[5] Besides its role in fibrotic diseases, PDGFs drive pathological mesenchymal responses in vascular disorders and retinal diseases.[4] Therein, the main cellular processes regulated by PDGFs are proliferation, differentiation, and migration of PDGF receptor (PDGFR)-expressing mesenchymal cells in physiological and pathological processes.

The PDGFs consist of highly conserved disulfide-linked homo- and heterodimeric growth factors (Figure 1, PDGF-AA, -AB, -BB, -CC, and -DD), which are structurally and functionally related to a larger growth factor family including vascular endothelial growth factor.[3,6] All isoforms are produced as inactive precursors. However, in contrast to PDGF-A and -B, which are activated already intracellularly by furin-like proteases, the isoforms PDGF-C and -D are secreted in a latent form with an N-terminal CUB (complement C1r/C1s, Uegf, Bmp1) domain.[4] The CUB domain needs to be extracellularly cleaved before the ligand can bind and activate its receptor. For CUB cleavage, different proteases have been identified, for example, the tissue-type plasminogen activator for PDGF-C or urokinase-type plasminogen activator for PDGF-D, but also others may be of physiological importance

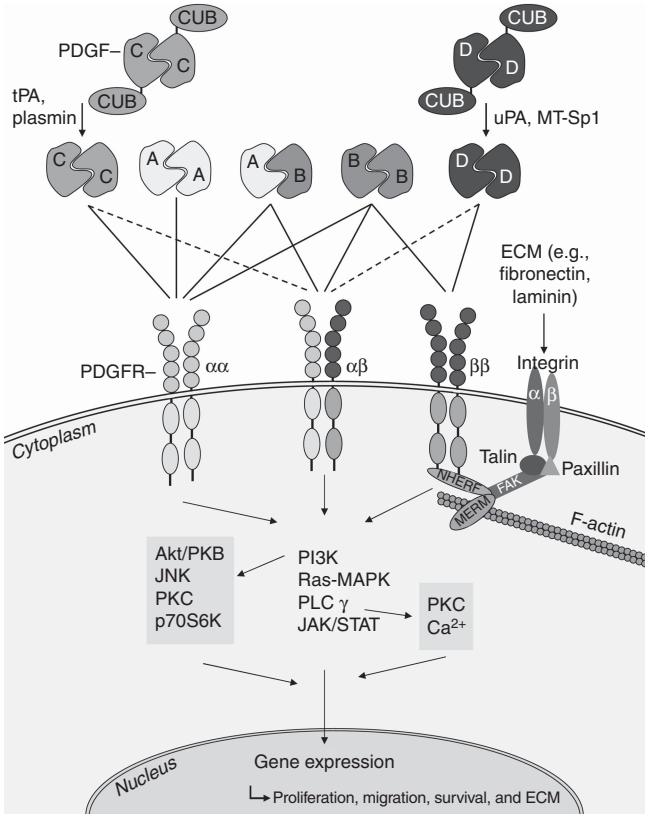

Figure 1 | Simplified scheme of the main molecules involved in PDGF–PDGFR interactions. PDGF -AA, -AB, and -BB are secreted in an active form, whereas PDGF-CC and -DD have to be proteolytically cleaved to allow binding of the ligands to their receptors. Proteases known to split off the PDGF-CUB domains are tPA or plasmin (PDGF-CC) and uPA or MT-Sp1 (PDGF-DD). For simplification of the scheme, many other regulatory processes, for example, processes limiting the PDGF response, are not included but mentioned in the text. Also not shown are the transactivation processes of PDGFRs without ligand binding by, for example, G-protein-coupled receptors. Akt/PKB, protein kinase B; CUB, complement C1r/C1s, Uegf, Bmp1; ECM, extracellular matrix; FAK, focal adhesion kinase; JAK, janus kinase; JNK, c-Jun amino-terminal kinase; MAPK, mitogen-activated protein kinase; MERM, merlin and ezrin/radixin/moezin family of cytoskeletal linkers; MT-Sp1, Matriptase; NHERF, Na+/H+ exchanger regulatory factor; p70S6K, ribosomal protein S6 kinase beta-1; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphatidyl-inositol-3-kinase; PKC, protein kinase C; PLC-γ, phospholipase C-γ; RAS, rat sarcoma; STAT, signal transducers and activators of transcription; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator. Figure with kind permission from Springer Science + Business Media (license date 12 September 2013) Ostendorf *et al.*[3]

(Figure 1).[3] PDGFRs are composed of PDGFR-α and/or -β chains, which dimerize upon ligand-binding (Figure 1). Whereas PDGF-AA binds to the PDGFR-αα-dimer only, PDGF-BB is a ligand for all receptors. The core domain of PDGF-CC binds to PDGFR-αα and -αβ, whereas PDGF-DD predominantly binds to PDGFR-ββ. Downstream signaling events for activated PDGFRs are similar, but not identical. PDGF binding results in autophosphorylation of the cytoplasmic tyrosine kinase domain of the PDGF receptor chains and subsequently recruits adaptor proteins carrying SH2 and SH3 domains to this site. Downstream signaling occurs mainly via the JAK/STAT, phosphoinositide 3-kinase, PLC-γ, or RAS–MAPK (mitogen-activated protein kinase) pathways, promoting gene expression and mediating the biological functions of the PDGF isoforms, for example, proliferation, migration, and survival. A highly relevant pro-fibrotic cross-talk is the cooperation of PDGF and integrin signaling. Na^+/H^+ exchanger regulatory factors were shown to link PDGFR-β with focal adhesion kinase and the cortical actin cytoskeleton, thereby enhancing PDGF-induced MAPK signaling. It is suggested that specificity of PDGFR signaling is achieved through a combination of cell type–specific expression and differential engagement of further downstream signaling pathways. For more details concerning PDGFR signaling, the reader is referred to Figure 1 and other reviews.[3,4,7]

All PDGF isoforms and their receptors are expressed early during kidney development, and all PDGF-A-, -B-, -C-, PDGFR-β-, or PDGFR-α-deficient mice die prenatally or very early during postnatal life.[6] For PDGF-C-deficient mice, this phenotype depends on the genetic background. Only double PDGF-A/C-deficient mice reproduce the phenotype of PDGFR-alpha-null mice, which is characterized by the lack of the renal interstitial mesenchyme. In contrast, PDGF-B- and PDGFR-β-deficient mice are mainly characterized by dysfunctional glomeruli with a specific lack of the mesangium. PDGF-D-deficient mice have not been described so far (reviewed in Floege *et al.*[6]).

RENAL EXPRESSION OF PDGFs AND THEIR RECEPTORS IN HEALTH AND DISEASE

The expression of PDGF ligands and receptors in normal postnatal human and rodent kidneys is well documented in many studies and has been previously reviewed by us in detail.[6] Both receptor chains are constitutively expressed by mesangial cells, fibroblasts, and vascular smooth muscle cells, but not by epithelial cells, such as visceral epithelial cells (podocytes) and tubular cells. Focal PDGFR-β expression, however, was reported for parietal epithelial cells,[6] and we demonstrated PDGFR-α expression by glomerular endothelial cells *in vitro*.[8] Renal expression of the PDGF ligands is less well defined, which is because of the variability of immunohistochemical approaches, species differences, and lack of reporter mice. Constitutive PDGF-A expression is detected in podocytes and epithelial cells of the distal nephron, whereas low levels of PDGF-B may be present in mesangial cells in normal mature glomeruli. PDGF-C and -D expression patterns reveal differences between species, for example, in rats PDGF-C is localized to arterial smooth muscle cells and epithelial cells of the collecting duct,[9] whereas in humans it has been localized to parietal epithelial cells, distal tubular epithelial cells, and arterial endothelial cells.[10] In humans, renal PDGF-D is constitutively expressed in podocytes and vascular smooth muscle cells, whereas expression in the rat kidney is restricted to vascular smooth muscle cells. PDGF-D expression in the mouse glomerulus is limited to mesangial cells.[11–13]