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A New Look at Platelet-Derived Growth Factor in Renal Disease

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ABSTRACT

The PDGF system, comprising four isoforms (PDGF-A, -B, -C, and -D) and two receptor chains (PDGFR-α and -β), plays important roles in wound healing, atherosclerosis, fibrosis, and malignancy. Components of the system are expressed constitutively or inducibly in most renal cells. They regulate a multitude of pathophysiologic events, ranging from cell proliferation and migration to extracellular matrix accumulation, production of pro- and anti-inflammatory mediators, tissue permeability, and regulation of hemodynamics. Genetic deletion of PDGF-B or PDGFR-β results in an absent glomerular mesangium, whereas PDGF-C and PDGFR-α contribute to the formation of the renal cortical interstitium. Almost all experimental and human renal diseases are characterized by altered expression of components of the PDGF system. Infusion or systemic overexpression of PDGF-B or -D induces prominent mesangioproliferative changes and renal fibrosis. Intervention studies identified PDGF-C as a mediator of renal interstitial fibrosis and PDGF-B and -D as key factors involved in mesangioproliferative disease and renal interstitial fibrosis. These data establish PDGF as one of the best characterized growth factors in renal disease and the most potent stimulus of mesangial cell proliferation currently identified. Accordingly, targeted intervention against the various PDGF isoforms offers a promising novel therapeutic approach to renal disease.

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PDGF is a mitogen and chemoattractant for mesenchymal cells. It is important in wound healing, atherosclerosis, organ fibrosis, and malignancy.[1–3] During the past 20 yr, considerable information on the role of the various PDGF family members in renal disease has accumulated. These data have been reviewed previously,[4] and this article primarily serves as an update with particular attention given to the discovery of PDGF-C and -D in 2000 and 2001, respectively, and to the delineation of their roles in renal pathophysiology.[2,3]

BIOCHEMISTRY OF PDGF AND PDGF RECEPTORS

PDGF-A and -B are secreted as homo- or heterodimers (Figure 1). The 14-kD B chain is encoded by the c-sis gene. PDGF-A occurs in two alternatively spliced versions. The longer 16-kD isoform is retained at the cell surface after secretion, whereas the shorter isoform is released into the extracellular medium.[5] PDGF-A and -B bind to various extracellular matrix proteins and may become more diffusible after cleavage of a COOH-terminal retention sequence.[1]

The two novel PDGF isoforms, PDGF-C and -D, are released as 55- and 49-kD homodimers, respectively.[6–8] Both are produced as latent factors, and extracellular cleavage of the complement subcomponent C1r/C1s, Uegf, and Bmp1 (CUB) domains is required for receptor binding and activation (Figure 1).[3] Tissue plasminogen activator is one identified specific PDGF-CC activating protease, whereas PDGF-DD is activated by urokinase-type plasminogen activator.[3] Excess free CUB domains might act as competitive antagonists for the full-length growth factors by interacting with their specific proteases.

PDGF receptors (PDGFR) are dimers composed of α and/or β chains. Whereas PDGF-A binds to the α chain only, PDGF-B is a ligand for all receptor types (Figure 1); however, at least in mesangial cells (MC), PDGF-B exerts its biologic activity almost exclusively *via* the PDGFR-$\beta\beta$ or PDGFR-$\alpha\beta$, despite expression of both receptor chains by the cells.[9,10] After proteolytic processing, the core domain of PDGF-CC seems to be largely a ligand for the PDGFR-α, whether present as the homodimer PDGFR-$\alpha\alpha$ or heterodimer PDGFR-$\alpha\beta$, whereas PDGF-DD binds predominantly to PDGFR-$\beta\beta$.[3]

PDGF SIGNALING

The PDGF receptor possesses tyrosine kinase activity and is autophosphorylated upon ligand binding.[1] The receptor

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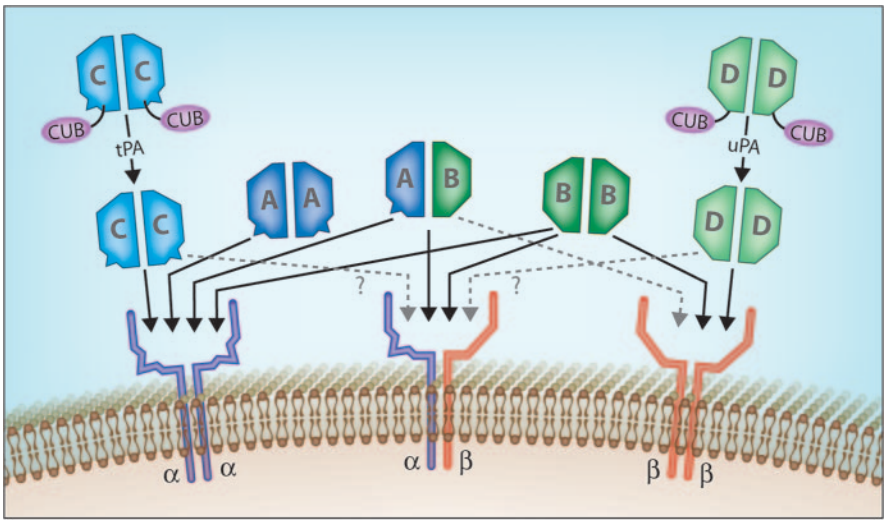

Figure 1. Schematic outline of the PDGF and PDGF receptor system showing the differential binding of the various PDGF isoform combinations to the PDGFR-α and -β chains. tPA, tissue plasminogen activator; uPA, urokinase-type plasminogen activator; CUB, complement subcomponent C1r/C1s, Uegf, and Bmp1 domain.

then interacts with several other cytoplasmic proteins containing SH2 domains, including phospholipase C, ras GTPase activating protein, phosphatidyl-inositol 3-kinase (PI3-K), members of the pp60src family of protein tyrosine kinase, tyrosine phosphatase SHP-2 and the Janus kinase/signal transducers and activators of transcription pathway.[1,11] Mutant mice expressing a PDGFR-β that can no longer activate PI3-K or phospholipase C-γ exhibit attenuated PDGF-dependent cellular functions but no reduction in survival.[12] Second messengers include inositol-1,4,5-triphosphate and diacylglycerol; intracellular calcium release; protein kinase C-α, -β, -ε, and -ζ; and prenylated, low molecular weight G proteins.[1,13,14] Mitogen-activated protein kinase (MAPK) is a downstream target of PI3-K.[15] Different MAPK, such as extracellular signal–regulated kinase, c-Jun N-terminal kinase, and p38, mediate different effector functions in MC, such as proliferation and TGF-β or chemokine synthesis in response to PDGF.[16] Inhibition of extracellular signal–regulated kinase *in vivo* indeed ameliorated mesangioproliferative nephritis.[17] PDGF-BB and angiotensin II (AngII) differ in their potency and duration of activation of the MAPK cascade, which may explain why PDGF-BB is a potent mitogen for MC, whereas AngII triggers only cell hypertrophy.[18] In the nucleus, PDGF signaling activates various proto-oncogenes and immediate early response genes, including c-fos, JunB, c-myc, and egr-1,[19,20] that are effectors of the receptor tyrosine kinase and responsible for particular downstream functions.[21]

Homodimeric $\alpha\alpha$ and $\beta\beta$ receptor complexes induce overlapping but distinctly different effects on target cells, which might be explained by differential interactions with various SH2 domain proteins. Autophosphorylation on different tyrosine residues might explain the unique properties of the heterodimeric $\alpha\beta$ receptor complex in comparison with homodimeric receptors. Finally, PDGF signaling can also be modulated in the extracellular milieu by matrix molecules. Naturally occurring PDGF antagonists include secreted, truncated receptor forms and α_2-macroglobulin.[1] The extracellular secreted protein, acidic and rich in cysteine binds PDGF-AB and -BB and thereby favors PDGF-AA bioactivity.[3]

STUDIES IN RENAL CELLS IN VITRO

In general, PDGF are major autocrine or paracrine mitogens and survival factors in many cells of mesenchymal origin.[10,22–27] PDGF synthesis is induced in cultured MC by various mediators, including PDGF itself, EGF, basic fibroblast growth factor, TNF-α, TGF-β, AngII, endothelin, thrombin, lipoproteins, lysophosphatidylcholine, phospholipids, and CpG nucleotides.[4,28–30] Many mitogens in fact exert their mitogenic effect through the induction of PDGF.[31,32] Negative regulators of PDGF synthesis have also been identified and include platelet factor-4 and NOV/CCN3.[33,34] In glomerular endothelial cells, hypoxia is another inducer of PDGF-B chain synthesis, whereas shear stress reduces it.[35,36] In proximal tubular cells, hyperglycemia is a strong stimulus for PDGF.[37] In these cells, growth factors such as hepatocyte growth factor and TGF-β, which are ultrafiltered in the glomerulus, may also act as PDGF inducers.[38]

Stimulation of MC with different PDGF ligands results in cellular proliferation and migration. In general, PDGF-AA exerts at best weak effects on MC proliferation.[39,40] In metanephric mesenchymal cells, PDGF-AA causes modest cell migration but has no effect on DNA synthesis.[41] In contrast, PDGF-BB stimulation of MC induces a rapid mobilization of intracellular calcium, decreases p27, and increases cyclin A and CDK2, resulting in pronounced cell proliferation.[39,40,42,43] MC migration in response to PDGF-BB involves upregulation of the cytoskeletal proteins moesin and radixin.[44] MC proliferation can also be induced by PDGF-CC and -DD.[9,25] In 3D culture, the MC responsiveness to PDGF decreases markedly as a result of PDGFR downregulation.[40] Mitogenic PDGF effects on other renal cell types are less consistent. PDGF does not affect proliferation in glomerular endothelial cells.[45] Tubular epithelial cells exhibit variable responses,[46,47] and papillary renal fibroblasts and to a lesser extent cortical fibroblasts respond with mitogenesis.[48]

PDGF also induce extracellular matrix synthesis in MC, parietal epithelial cells, and, to a lesser degree, tubular epithelial cells.[49–53] They may affect this by acting upstream of and/or in con-

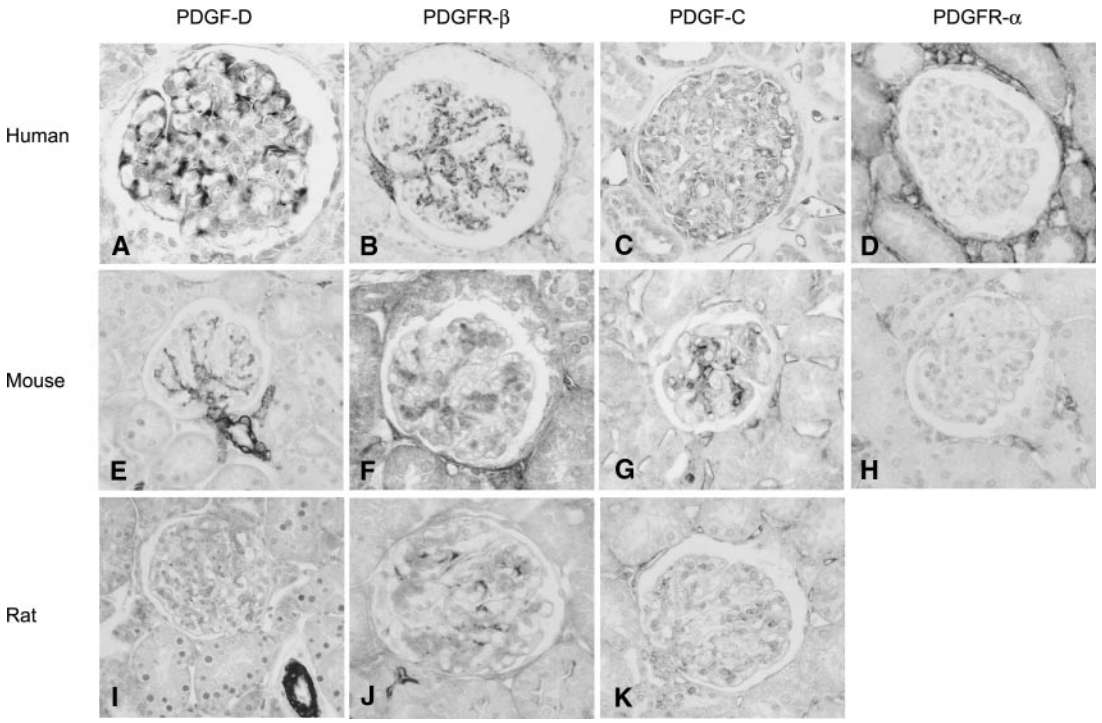

Figure 2. Immunohistochemical localization of PDGF-D and its receptor PDGFR-β and of PDGF-C and its principle receptor PDGFR-α in human (A through D), mouse (E through H), and rat (I through K) glomeruli. Constitutive expression of PDGF-D is localized to podocytes in humans and MC in mice and is not detected in rat glomeruli. VSMC in all of these species express PDGF-D (E and I). PDGFR-β is expressed by MC and interstitial cells in all of these species. Expression of PDGFR-β by parietal epithelial cells is best seen in the human (B). PDGF-C is constitutively expressed in mouse MC and by microvascular endothelial cells in all three species. Although not visualized in this preparation, expression of PDGF-C by parietal epithelial cells has been reported. PDGFR-α is not normally detectable in human or mouse glomeruli but is expressed by interstitial cells. Studies of PDGFR-α expression in normal adult rat glomeruli are not available.

cert with other cytokines such as TGF-β.[52,54,55] In contrast to TGF-β, PDGF exhibits little effect on matrix degradation.[56,57]

PDGF-BB stimulation of MC leads to an increased expression of numerous mediators of disease and inflammation, including TGF-β1, CCL-2, CXC3CL1, plasminogen activator inhibitor-1, IL-6, endothelin-1, inducible nitric oxide synthase, and YB-1.[4,16,58–61] Through effects on MC contraction and prostanoid production, PDGF also contributes to the regulation of glomerular hemodynamics. Infusion of PDGF into isolated microperfused glomeruli increases intraglomerular pressure and vascular resistance and decreases flow rate.[62–64]

Finally, PDGF affects very-low-conductance Ca^{2+}-permeable channels,[65–67] which regulate intracellular calcium and thereby prevent apoptosis in MC,[68] as well as the permeability of intercellular tight and gap junctions in tubular cells and MC, respectively.[69,70] These latter effects may also contribute to the increased tissue permeability that is a characteristic of several kidney diseases.

NORMAL DISTRIBUTION IN EMBRYONIC AND ADULT RODENT AND HUMAN KIDNEY

Early in metanephric kidney development, PDGFR-α and -β are expressed in the undifferentiated blastema, vascular structures (PDGFR-β only), and interstitium.[71,72] mRNA encoding PDGFR-α is present in some mesangial structures in early glomeruli but is largely lost as glomeruli mature.[72] During the transition from S-phase vesicles to identifiable glomeruli, PDGFR-β is expressed uniformly by cells differentiating into MC.[72] In developing metanephric kidney, PDGF-B chain is expressed by the differentiating epithelium of early-stage glomerular vesicles (comma and S stage), but in later stages of glomerular development, the expression of PDGF-B chain is limited to MC.[72] PDGF-D expression has been identified in the epithelial cells of comma- and S-shaped vesicles and in the visceral epithelial cells of later stage glomeruli in developing human kidneys.[73]

The localization of PDGF-A and -B and PDGFR-α and -β in postnatal human and rodent kidneys has been well established (Table 1). PDGFR-α is widely expressed by renal interstitial cells and to some degree by MC.[71] Constitutive PDGFR-α expression by smooth muscle cells of the renal arterial vasculature has been identified but is not uniform among these cells. PDGFR-β is expressed postnatally by MC, glomerular parietal epithelial cells, and interstitial cells.[74]

Table 1. Expression of PDGF and PDGFR in normal adult kidney of various species[a]

Parameter	PDGF-A	PDGF-B	PDGF-C	PDGF-D	PDGFR-α	PDGFR-β
Glomerulus					+ h[141]	+ h[141]
endothelial cells	−	−	+ m[78]	−	−	−
MC	−	−	+/− h[142]	+/− m, r, h[26,73,78]	+ m, h[71,143]	+ m, h[74,78]
podocytes	+ h[75]	−	−	+ h[73]	−	−
parietal epithelial cells	−	−	+/− h[77]	−	−	+ h[74]
Arteries						
smooth muscle cells	+ m, h[75,76,78]	+ m[78]	+ m, r, h[25,78,142]	+ m, h[73,78]	−	−
endothelial cells	+ h[75]	−	+/− m, h[77,78]	−	−	−
Tubules						
proximal tubules	−	−	−	−	−	−
distal tubules	+ m, h[75,76]	−	+/− h[77]	−	−	−
collecting ducts	+ h[75]	−	+ r, h[25,77]	−	−	−
Interstitium					+ h[141]	+ h[141]
interstitial cells	−	−			+ m, h[71,76,78]	+ m, h[74,76,78]

[a]−, not expressed; +/−, inconsistent, species-specific, and/or controversial results; + expressed; h, human; m, mouse; r, rat.

PDGF-A chain is normally expressed by mature podocytes and epithelial cells of the distal nephron, including collecting ductal cells and urothelium.[75] In the mouse, PDGF-A chain also seems to be expressed by cells of the loop of Henle.[76] Although low levels of PDGF-B chain expression by MC in normal mature glomeruli may be present, it has been difficult to detect constitutive expression by these cells using immunohistochemistry.

Localization of the more newly recognized PDGF isoforms has been hampered by the limited availability of reliable reagents. Important differences in patterns of expression in mouse, rodent, and human kidneys have been revealed (Figure 2, Table 1). PDGF-C has been localized to arterial smooth muscle cells and collecting duct epithelial cells in the rat. In humans, PDGF-C has been localized to parietal epithelial cells in the glomerulus, tubular cells from all parts of the nephron distal to the proximal tubules, and arterial endothelial cells.[25,77] In normal human adult kidneys, PDGF-D expression persists in podocytes and is constitutively expressed by vascular smooth muscle cells (VSMC).[73] Constitutive expression of PDGF-D in the rat is limited to VSMC only.[26] In the mouse, PDGF-D is constitutively expressed in glomeruli but by MC and not podocytes in contrast to humans.[78]

INSIGHT INTO RENAL DEVELOPMENT OBTAINED FROM GENETICALLY ALTERED MICE

Genetically altered mice can provide important clues to the developmental role of individual proteins and can provide clues to pathogenetic processes during renal disease in adult animals. PDGF-A$^{-/-}$ mice usually die on embryonic day 10. Postnatally, surviving mice develop lung emphysema but no renal abnormalities.[79] PDGF-C$^{-/-}$ mice have been reported to die in the perinatal period and exhibit a complete cleft of the secondary palate.[6] Mice with combined homozygous deficiency for PDGF-A and -C among other defects lack elements of the renal cortical interstitium and largely seem to mirror the phenotype of mice deficient for PDGFR-α.[80] These observations point to potential roles of PDGF-A and -C and/or PDGFR-α in mediating renal interstitial disease, a notion that was recently confirmed by us (see Intervention Studies).

Mice deficient for PDGF-B also die perinatally. The most notable abnormality is an absence of normal glomerular tuft formation as a result of a complete lack of MC migration into the glomerular stalk, whereas glomerular endothelial cells, the basement membrane, and podocytes are largely preserved. Most PDGF-B mutant embryos also develop fatal hemorrhages as a result of disturbed arterial pericyte formation and function.[81–83] An almost identical renal phenotype results from genetic ablation of PDGF-B in endothelial cells only,[84] in PDGFR-β–deficient mice,[85] or when an antagonistic anti–PDGFR-β mAb was administered to neonatal mice, where outer cortical glomeruli still form after birth.[86] Finally, when the matrix retention motif within the PDGF-B molecule was deleted in mice, delayed formation of the mesangium was again noted and resulted in proteinuria and glomerulosclerosis.[87]

Whereas PDGF-D null mice have not been described yet, its overexpression using a metallothionein promoter resulted in no gross pathologic renal changes on embryonic day 15, but no live transgenics were born (W. LaRochelle, PhD, and M.J. Jeffers, PhD, Curagen Corp., Branford, CT, personal communication, February 27, 2007). When we specifically overexpressed PDGF-D in podocytes of mice, intraglomerular pathology ranging from mesangioproliferative lesions to crescentic glomerulonephritis evolved.[88]

Collectively, these observations point to central and nonredundant roles of PDGF-B and -D and PDGFR-β in the development of the glomerular mesangium. The effects of PDGF-B and, by implication, PDGF-D and PDGFR-β interactions that allow development of a mesangium are recapit-

ulated in mesangial regeneration after mesangiolytic injury and in mesangioproliferative responses to injury in mature rats (see Intervention Studies). With respect to therapeutic interventions in renal patients, additional data are of major importance: Transgenic high-level overexpression of a soluble PDGF-B and -D antagonist (soluble PDGFR-β) in the liver during late embryogenesis and throughout postnatal life in mice was not associated with any phenotype.[89] This suggests that, in contrast to embryogenesis, PDGF-B and -D are not required during normal adult life.

EXPRESSION OF PDGF AND PDGFR IN RENAL DISEASE

Upregulated PDGF expression has been observed in a large number of rodent injury models, including mesangioproliferative anti–Thy 1.1 glomerulonephritis, AngII-induced renal damage, nephrotoxic nephritis, puromycin-induced FSGS, diabetic nephropathy, renal transplantation, ischemia/reperfusion, murine lupus nephritis, and murine IgA nephropathy. Studies examining the PDGF expression in human renal tissues have focused on a similar spectrum of renal diseases (Table 2).

PDGF-A was overexpressed within MC in models of mesangioproliferative glomerulonephritis and within endothelial and smooth muscle cells during human vascular transplant rejection.[90,91] In animal models, PDGF-C was upregulated in MC and podocytes upon cellular injury and/or activation and within the interstitium at sites of renal fibrosis.[25] In human renal biopsies, PDGF-C overexpression was prominent in podocytes of membranous nephropathy as well as transplant glomerulopathy and again at sites of interstitial fibrosis.[77] An upregulation of PDGFR-α has been shown in VSMC and in tubulointerstitial cells in the course of different renal diseases.[78,92]

Numerous publications have reported an overexpression of PDGF-B in the course of renal diseases. Upregulation of PDGF-B has been reported in MC, VSMC, tubular cells, interstitial cells, and, in rare instances, podocytes in animal models and human renal diseases (Table 2).[90,93–97] The renal expression of PDGF-D is comparably less well characterized, but an upregulation has been detected in experimental mesangioproliferative glomerulonephritis and in interstitial cells in the course of renal fibrosis.[26,78] Renal PDGFR-β overexpression has been detected in MC but also in parietal epithelial cells, endothelial cells, tubular epithelial cells, and interstitial cells.[74,98–102]

Table 2. Regulation of PDGF and PDGFR in renal disease[a]

Parameter	PDGF-A	PDGF-B	PDGF-C	PDGF-D	PDGFR-α	PDGFR-β
Animal models						
glomerulus[b]	+[144]	+[94,98,144–155]			+[90]	+[98,146,151]
endothelial cells						
MC	+[90]	+[90,94,95,146,152,153]	+[25]	+[26]		+[90,146]
podocytes		+[93,146]	+[25]			+/−[93,146]
parietal epithelial cells		+[152,154]				+[154]
circulating leukocytes, platelets		+[95,152]				
arteries[b]		+[155]				
smooth muscle cells			+/−[25]			
endothelial cells						
tubules[b]		+[78,96,99,156]			+[97]	+[97]
interstitium[b]		+[99,157]			+[78]	+[78,99,156]
interstitial cells	+[158]	+[78,99]	+[25]	+[78]	+[78]	+[78,156]
macrophages			+[25]			
Human renal diseases						
glomerulus[b]	+[159]	+[100,153,159–164]	+[77]		+[92,141]	+[100,101,141,160,162,164,165]
endothelial cells			+/−[77]			
MC			+/−[77]		+/−[92]	
podocytes			+[77]			
parietal epithelial cells						
arteries[b]		+[161]				+[141]
smooth muscle cells	+[92]	+[91]			+[92]	+[165]
endothelial cells	+[92]					
tubules[b]		+[166]		+[73]		
interstitium[b]		+[78,164]	+[77]	+[78]	+[92,141]	+[78,141,159,165]
interstitial cells		+[78,164]	+[77]	+[78]	+[92]	+[78,164,165]
macrophages		+[91]				

[a]Expression in comparison with normal kidney: +/−, limited to a few models/diseases or controversial results; +, upregulation. Empty boxes denote lack of data or no change in expression from normal (see Table 1).
[b]Cell type not specified.

OVEREXPRESSION OR PHARMACOLOGIC ADMINISTRATION

Various studies have investigated the renal consequences of infusing or overexpressing the different PDGF isoforms *in vivo*. Infusion of even very high dosages of PDGF-AA (5 mg/kg) into healthy rats failed to induce renal pathology.[103] Similarly, adenoviral transfection of mouse liver with a construct encoding PDGF-C and causing elevated circulating levels of this isoform did not induce renal abnormalities.[104] A novel biologic role of PDGF-C, which has yet to be explored in the kidney, is a very potent induction of angiogenesis.[105]

Infusion of recombinant PDGF-BB into healthy rats led to a selective increase of glomerular MC proliferation.[106] PDGF-induced MC proliferation and mesangial matrix accumulation were markedly augmented when the MC had suffered a minor (subclinical) injury before the PDGF infusion.[106] Administration of PDGF-BB to hyperglycemic GK rats also resulted in acute, transient MC proliferation and activation.[107] The induction of mesangioproliferative changes was reproduced in healthy mice and rats by hepatic transfection with viral constructs encoding PDGF-B, resulting in elevated circulating levels of this isoform.[104] Finally, glomerular overexpression of PDGF-B also drove bone marrow–derived cells toward a mesangial-like phenotype *in vivo*.[108] At very high dosages (5 mg/kg), PDGF-BB infusion into rats induced dosage-dependent renal tubulointerstitial cell proliferation, myofibroblast formation, and fibrosis, which were reversible after PDGF-BB infusion was abrogated.[103]

Mice with high circulating levels of PDGF-D after adenoviral transfection of the liver developed a severe mesangioproliferative glomerulopathy, characterized by enlarged glomeruli and a striking increase in glomerular cellularity.[104] Collectively, these data demonstrate potent roles of PDGF-B and -D in inducing mesangioproliferative changes as well as tubulointerstitial fibrosis in the case of PDGF-B.

INTERVENTION STUDIES

Little is known on the effects of PDGF-A inhibition *in vivo* (Table 3). PDGF-A chain antisense oligonucleotides improved arterial and renal damage in stroke-prone spontaneously hypertensive rats.[109] Antagonism of PDGF-C using a neutralizing antiserum reduced the extent of renal tubulointerstitial fibrosis after unilateral ureter ligation.[110] These studies complement other studies in which cardiac overexpression of PDGF-C induced myocardial fibrosis.[111]

Various interventions that reduce MC proliferation *in vivo*, such as administration of heparin, C-type natriuretic peptide, or antisense oligonucleotides against Egr-1, may act indirectly through inhibition of autostimulatory effects of endogenously produced PDGF. Each of

Table 3. Effects of PDGF antagonism in models of renal disease[a]

Model	Intervention	Effects	Reference
Spontaneously hypertensive rats	PDGF-A antisense oligonucleotides	↓ renal damage	109
Murine unilateral ureteral obstruction	Neutralizing anti–PDGF-C antiserum	↓ tubulointerstitial fibrosis and leukocyte influx	110
Rat acute antithymocyte serum GN	Neutralizing anti–PDGF-AB IgG	↓ MC proliferation and matrix accumulation	116
Rat acute anti–Thy 1.1 GN	Transfection of cDNA encoding the extracellular domain of PDGFR-β fused with IgG-Fc	↓ MC proliferation and matrix accumulation	118
Rat acute anti–Thy 1.1 GN	Anti–PDGFR-β IgG	↓ MC proliferation and matrix accumulation	119
Rat acute anti–Thy 1.1 GN	B-specific oligonucleotide aptamer	↓ MC proliferation and matrix accumulation	117
Rat chronic anti–Thy 1.1 GN	B-specific oligonucleotide aptamer	↓ proteinuria, ↑ renal function, ↓ glomerulosclerosis and tubulointerstitial fibrosis	122
Rat acute anti–Thy 1.1 GN	Neutralizing anti–PDGF-D IgG	↓ MC proliferation and matrix accumulation	26
Rat chronic anti–Thy 1.1 GN	Neutralizing anti–PDGF-D IgG	± proteinuria, ↑ renal function, ↓ glomerulosclerosis and tubulointerstitial fibrosis, ↓ EMT	123,124
Rat acute anti–Thy 1.1 GN	Trapidil	↓ MC proliferation and matrix accumulation	126
Rat acute anti–Thy 1.1 GN	Imatinib	↓ MC proliferation and matrix accumulation	131,132
Rabbit nephrotoxic nephritis	Trapidil	Trend toward worse clinical data and renal histology	127
Murine streptozotocin-induced diabetes	Imatinib	↓ albuminuria, glomerular and tubulointerstitial damage	133
Murine lupus	Imatinib	↑ survival, ↓ proteinuria, ↓ glomerular and tubulointerstitial damage	134
Rat unilateral ureter obstruction	AG 1295	↓ tubulointerstitial fibrosis	136
Rat ischemia/reperfusion injury	Trapidil, Ki6896	↑ serum creatinine, ↑ mortality rate, ↓ proliferation of tubular epithelial cells	97

[a]EMT, epithelial-to-mesenchymal transition; GN, glomerulonephritis.

these interventions also led to reduced glomerular expression of PDGF-B chain.[112–114] Similarly, aminoguanidine reduced glomerular PDGF-B overexpression and matrix accumulation in streptozotocin-induced rodent diabetes.[115]

A number of specific interventions aimed at neutralizing PDGF-B or -D or blocking the PDGF-β receptor have been shown to reduce MC proliferation and matrix accumulation in rat anti–Thy 1.1 mesangioproliferative glomerulonephritis (Table 3),[26,116–119] whereas glomerular endothelial cell proliferation was not affected.[120] PDGF-B antagonism in this model did not affect the TGF-β system, suggesting that PDGF-B acts downstream or independent of TGF-β and may thus be a specific target to ameliorate both increased cellularity and matrix production.[121] More important, transient PDGF-B or -D antagonism during the mesangioproliferative phase of progressive anti–Thy 1.1 glomerulonephritis prevented the subsequent development of renal failure and glomerular as well as tubulointerstitial scarring.[122,123] Beneficial effects of anti–PDGF-D treatment were observed even when treatment started after the acute mesangioproliferative phase, suggesting that PDGF-D antagonism also has a role in retarding tubulointerstitial fibrosis.[124] A role for PDGF-D in fibrotic disease is also suggested by the finding of cardiac fibrosis after heart-specific overexpression.[111]

Trapidil, a nonspecific PDGF antagonist, markedly reduced PDGF-BB–induced proliferation of MC *in vitro*[125] and *in vivo*[126]; however, in rabbit accelerated nephrotoxic nephritis and in rats with renal ischemia/reperfusion injury, clinical and histologic data worsened in trapidil-treated animals.[97,127] Other drugs that are used in patients with renal disease, including calcium channel blockers, lovastatin, and ramipril, also interfere with PDGF signaling, but it is unknown whether the beneficial effect of these drugs may be partly due to PDGF inhibition.[128–130]

A number of low molecular weight PDGF receptor tyrosine kinase blockers have been evaluated in renal disease (Table 3). Some caution is necessary when interpreting these studies, because many of the kinase blockers exhibit only relative specificity for the PDGF receptor, and some, such as the c-abl kinase inhibitor imatinib (STI 571), were developed primarily to inhibit other kinases and only reduce PDGFR-α and -β signaling as a "side effect." Ki6896, like trapidil, worsened rat renal ischemia/reperfusion injury.[97] In contrast, in all other injury models tested, blockade of the PDGFR tyrosine kinase was beneficial. Thus, imatinib reduced mesangioproliferative changes in experimental glomerulonephritis[131,132]; mildly ameliorated both renal functional and structural parameters in diabetic apolipoprotein E knockout mice[133]; improved survival, renal function, and histology in murine lupus[134]; and prevented chronic allograft nephropathy after rat kidney transplantation.[135] Finally, another PDGF tyrosine kinase inhibitor, AG 1295, mildly delayed the development of interstitial fibrosis in rats with unilateral ureteral obstruction[136]; however, at least in the case of imatinib, it is not always clear whether the benefit observed related to inhibition of the PDGFR tyrosine kinase or to inhibition of the c-abl kinase, which also contributes to renal interstitial fibrosis.[137] In addition, significant adverse effects of imatinib on the myocardium have been related to inhibition of the c-abl kinase rather than the PDGFR tyrosine kinase.[138]

Taken together, these data provide strong evidence that inhibition of PDGF-B and -D can be an effective approach to proliferative glomerulonephritis and that both can also directly or indirectly affect the progression of renal tubulointerstitial damage. Recent evidence also suggests a beneficial effect of PDGF-C antagonism in the latter process.[110] At least two studies suggested that PDGF inhibition should be avoided in instances of ischemia-reperfusion injury of renal tubules.[97] Although the potential benefits of PDGF blockade in human renal disease is not yet known, it is noteworthy that specific inhibition of PDGFR-β in normal volunteers so far has shown a good safety profile, whereas in some patients with tumors, fluid retention and ascites has been noted.[139]

CONCLUSIONS

From the wealth of data discussed, it is obvious that PDGF is one of the best-characterized growth factor systems in renal disease. Altered expression of PDGF and/or its receptors is involved in most renal diseases and is an essential component of mesangial and interstitial proliferation and responses to injury. Specific anti-PDGF interventions can prevent important long-term sequelae in experimental models of renal disease. An obvious first human disease to test anti-PDGF therapy is mesangioproliferative glomerulonephritis, in particular IgA nephropathy. Specific anti-PDGF compounds have been developed and tested in humans, including CDP860, a humanized, PEGylated di-Fab′ that blocks the PDGFR-β, and CR002, a fully human mAb to PDGF-D.[139,140] Clearly, the time is ready for clinical trials of PDGF intervention. Imatinib, already approved for human use as an antineoplastic agent, is a candidate therapeutic agent for this purpose, but later generation tyrosine kinase inhibitors are being tested for potentially better safety profiles.

Which research areas merit further studies in this field? Effects of anti-PDGF therapy in other renal diseases, in particular diabetic nephropathy and lupus nephritis, have not been well characterized so far. Another field that has received little attention is the regulation of PDGF bioactivity in renal disease. We have characterized a PDGF-regulated downstream antagonist, NOV/CCN3,[34] and others may exist and be useful targets for pharmacologic intervention. Uncharted territory also relates to the proteolytic activation of the novel PDGF-C and -D isoforms in renal disease as well as the role of matrix binding of PDGF in the kidney. Finally, novel activities such as the angiogenic properties of PDGF-CC may merit exploitation in models of thrombotic microangiopathy.

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