Progressive renal diseases represent a global medical problem, in part because we currently lack effective treatment strategies. Inhibition of platelet-derived growth factors (PDGFs) might represent one such novel strategy. PDGFs are required for normal kidney development by the recruitment of mesenchymal cells to both glomeruli and the interstitium. PDGFs are expressed in renal mesenchymal cells and, upon injury, in epithelial and infiltrating cells. They exert autocrine and paracrine effects on PDGF receptor-bearing mesenchymal cells, i.e. mesangial cells, fibroblasts and vascular smooth-muscle cells, which are crucially involved in progressive renal diseases. Proliferation but also migration and activation of these mesenchymal cells are the major effects mediated by PDGFs. These actions predefine the major roles of PDGFs in renal pathology, particularly in mesangioproliferative glomerulonephritis and interstitial fibrosis. Whereas for the former, the role of PDGFs is very well described and established, the latter is increasingly better documented as well. An involvement of PDGFs in other renal diseases, e.g. acute kidney injury, vascular injury and hypertensive as well as diabetic nephropathy, is less well established or presently unknown. Nevertheless, PDGFs represent a promising therapeutic option for progressive renal diseases, especially those characterized by mesangial cell proliferation and interstitial fibrosis. Clinical studies are eagerly awaited, in particular, since several drugs inhibiting PDGF signalling are available for clinical testing.

Keywords: chronic kidney disease, fibroblasts, fibrosis, mesangial cells, platelet-derived growth factors

INTRODUCTION

Some epidemiological studies have suggested a prevalence of moderate-to-advanced chronic kidney disease (CKD) of >10% in the general population [1]. The uncovering of molecular mechanisms which would allow both a specific treatment of the primary renal disease as well as of the common processes promoting CKD is therefore of great interest. Such common processes include, in particular, renal fibrosis, i.e. an essential process of wound healing, probably even in the kidneys which becomes pathological if left unchecked [2]. Blocking renal fibrosis is a highly attractive therapy for CKD patients and has raised considerable interest from pharmaceutical companies, especially since antifibrotic therapies may, of course, have implications far beyond the kidney. Unfortunately, however, the translation of new treatment options has been rather poor in nephrology, the reasons being manifold [3].

In this review, we discuss the role of the platelet-derived growth factor (PDGF) family of proteins in renal diseases, with a particular focus on progressive renal diseases.

PDGF & PDGF RECEPTORS

PDGF was first described by Ross et al. in 1974 as a ‘a platelet-dependent serum factor that stimulates the proliferation of...
arterial smooth-muscle cells in vitro' [4]. Since then, tremendous progress has been made in our understanding of the role of PDGFs, which reaches far beyond the role in vascular smooth-muscle cell proliferation [5]. PDGFs are involved in the embryonic development of many organs including the brain, lungs, vasculature and kidneys (see below) [6]. Proliferation, differentiation and migration of mesenchymal cells, which are the major PDGF receptor (PDGFR)-bearing cells, are the main processes regulated by PDGFs both during development and adulthood and in both physiological and pathological processes. Best characterized is the role of PDGFs in the vascular system. PDGFs are essential for physiological angiogenesis by the recruitment of perivascular cells, e.g. pericytes, but they are also involved in the regulation of vascular tone and platelet aggregation [5]. PDGFs play crucial roles in cardiovascular diseases, e.g. during vessel remodelling or atherosclerosis. Both latter processes are also important factors in progressive renal diseases of native or transplanted kidneys. We will not cover these processes within this review, in part because hardly any data exist specifically for the kidneys [7]. PDGFs were also shown to be involved in tumourigenesis, by direct pro-oncogenic effects but also by indirect effects on tumour angiogenesis and tumour stroma. Finally, PDGFs are involved in wound healing and its pathological counterpart, organ fibrosis [8, 9].

PDGFs comprise five dimers (PDGF-AA, -AB, -BB, -CC and -DD) with distinct binding affinity to three dimeric PDGFRs with tyrosine-kinase activity (PDGFR-αα, -αβ and -ββ). PDGFR-αα-specific ligands include PDGF-AA and -CC, the latter being a low-affinity ligand for -αα receptor as well. PDGF-BB and -AB bind to all three receptor dimers. PDGF-DD is the only specific high-affinity ligand for PDGFR-ββ and, as PDGF-CC, a low-affinity ligand for the ββ receptor (Figure 1). The binding of PDGFs to the PDGFRs induces downstream signalling involving several well-known pathways, e.g. Ras-MAPK, PI3K, PLC-γ pathways and others (Figure 1). For more detailed description of these downstream pathways, we refer the readers to several excellent review articles [5, 10–12].

Historically, the first described isoforms were the ‘classical’ PDGFs -AA, -BB and -AB. PDGF-CC and -DD were described >20 years later, in 2000 and 2001, respectively. PDGF-CC and -DD differ from the ‘classical’ PDGF isoforms in that they are secreted in an inactive form containing an N-terminal CUB domain, and they lack a C-terminal basic sequence involved in binding to extracellular matrix in ‘classical’ PDGF isoforms. Proteolytic cleavage of the CUB domain is required for receptor binding. Proteases identified in the CUB domain cleavage include tissue plasminogen activator (tPA) for PDGF-CC, urokinase plasminogen activator (uPA) for PDGF-DD and plasmin for both isoforms (Figure 1) [13]. CUB domains are found on various proteins, e.g. complement, and exert various functions, e.g. calcium binding and interaction with various ligands [14]. To date, we have no data on the role of CUB domains in the kidneys, neither in those derived from PDGFs nor from others. The function of the PDGF-AB isoform and the receptor αβ also remains largely unknown. This is mainly due to methodological difficulties in specifically dissecting their role from the other isoforms. It also remains largely unclear whether the isoforms with overlapping receptor binding, i.e. -BB and -DD and -AA and -CC, have different roles or can substitute for each other. In fact, using genomic and proteomic approaches, we have shown that PDGF-BB and -DD in mesangial cells and -AA and -CC in renal fibroblasts exerted nearly identical effects [15, 16].

Several factors influencing PDGF signalling have been described. These include the proteases activating PDGF-CC and -DD (described above), proteases cleaving the extracellular matrix retention motive in ‘classical’ PDGF isoforms or proteases degrading PDGF-BB, e.g. factor VII-activating protease. Molecules like SPARC (secreted protein, acidic and rich in cysteine/ BM40/osteonectin) were shown to inhibit PDGFR binding. Integrins may act as co-receptors and G-protein-coupled receptor as transactivators of PDGFR signalling [5, 12]. Other endogenous PDGF antagonists might be the nephroblastoma overexpressed (NOV, CCN3) or Dickkopf-related protein 1 (Dkk-1), see below.

### RENAL PDGF AND PDGFR EXPRESSION

Renal expression of PDGFs and their receptors is well documented by several studies and has been reviewed in detail by us previously [11]. As in other organs, kidney mesenchymal cells, i.e. glomerular mesangial cells, interstitial fibroblasts and vascular smooth-muscle cells, constitutively express both PDGFR-αα and -ββ (Figure 2). PDGFR-ββ is even being used as a marker for these mesenchymal cells. The PDGFR expression is maintained in vitro and renders these cells responsive to PDGFs. Epithelial cells, such as podocytes and tubular cells, do not express PDGF receptors in normal nor in pathological conditions. Some focal expression of PDGFR-ββ was described on parietal epithelial cells. PDGFRs were also not observed on glomerular endothelial cells in vivo. However, we found that in vitro glomerular endothelial cells expressed PDGFR-αα and were responsive to PDGF-CC [17]. These data are in line with reports of low PDGF expression on the microvascular endothelium [18]. It remains to be shown whether PDGFRs are expressed in vivo on the renal endothelium of peritubular capillaries (Figure 2). It also remains unclear whether resident macrophages or dendritic cells of the kidney express PDGFR.

The expression of the PDGFR ligands is less well characterized. This mainly relates to difficulties and some variability in the immunohistochemical detection of PDGFs, species differences and lack of reporter mice. Vascular smooth-muscle and mesangial cells seem to express all PDGF isoforms, although the data are somewhat variable between species and diseases [11]. PDGF-DD is expressed by podocytes, and focally by parietal epithelial cells, in humans, but mainly by mesangial cells in mice [19]. PDGF-CC was also observed in parietal epithelial cells in humans and in the developing mesangium [20].

In the tubulointerstitium, PDGF-AA, -CC and -DD were described to be expressed in some tubular cells and collecting ducts. Upon injury, PDGF-BB and -DD are highly and in part de novo expressed in tubular cells [11, 21–23], whereas PDGF-CC seems to be mainly expressed in infiltrating macrophages [21, 24].

Whether PDGF isoforms are expressed in renal endothelial cells, and if so in which ones, remains largely unclear.
Endothelial-specific ablation of PDGF-BB documented the importance of endothelium-derived PDGF-BB for glomerular development [25]. Glomerular endothelial cells in mice express PDGF-CC [23], and our study suggested paracrine and autocrine effects of PDGF-CC in glomerular endothelial cells [17]. Some studies suggested endothelial expression of both PDGF-AA and -CC [11]. It is conceivable that, as in other organs, PDGFs are expressed in the renal endothelium and might be involved in renal angiogenesis, being physiological or pathological. Taken together, renal mesenchymal cells are the main PDGFR-bearing cells and also the main PDGF effector cells via paracrine and autocrine signalling. The expression of PDGFs in endothelial and epithelial cells remains less well characterized.

**PDGFs and Their Receptors in Renal Development**

PDGFs are essential for kidney development by the recruitment of mesenchymal cells. Mice with genetic deletion of
PDGFR-β, PDGF-BB or endothelium-derived PDGF-BB showed a similar renal phenotype with failure to develop a glomerular mesangium [25–28]. PDGF-AA-deficient mice showed no obvious renal phenotype [29]. On the other hand, PDGFR-α and combined PDGF-AA- and -CC-deficient mice exhibited similar renal phenotypes with failure to develop an interstitium [30]. PDGF-CC-deficient mice develop a complete cleft palate [31], however, if bred on different genetic backgrounds (e.g. C57Bl6) they are viable and show no obvious renal phenotype, at least until early adulthood ([24] unpublished observations). PDGF-DD-deficient mice were not yet described, but preliminary experiments showed that these mice are viable and have no obvious renal phenotype (own unpublished results). These latter observations suggest that other isoforms can compensate for an ontogenetic lack of PDGF-CC and -DD. Both PDGF-BB and -AA induced chemotaxis of metanephric mesenchyme, and interestingly, the PDGF-BB signal seemed to inhibit that of PDGF-AA [32]. Taken together, during development, the PDGFR-β-PDGF-BB axis is essential for the recruitment of mesangial cells and PDGFR-α as well as PDGF-AA and -CC for the recruitment of interstitial cells.

Apart from their role in embryogenesis, potential roles of PDGFs in physiological processes in the adult kidney remain elusive. Long-term deletion of PDGFR-β in adult mice resulted in reduced ageing-dependent mesangial expansion but also in defective adaptation to glomerular hypertrophy [33], suggesting a potential role in mesangial homeostasis.

**PDGFs in Renal Pathology**

Several studies analysed the role of PDGFs in animal models of renal diseases, in particular regarding mesangial proliferation and interstitial fibrosis.
Mesangioproliferative glomerulonephritis and mesangial sclerosis

PDGFR-β and its ligands PDGF-BB and -DD are crucial mediators of mesangial cell proliferation. This is the best described role of PDGFs in renal diseases and several lines of evidence support this [11, 34]. First, the receptor (Figure 2) and its ligands are overexpressed in mesangioproliferative diseases [11]. Secondly, both ligands potently induce mesangial cell proliferation in vitro [11, 34, 35]. Thirdly, overexpression of both ligands systemically or of PDGF-DD in podocytes in healthy mice, was sufficient to induce mesangioproliferative glomerulonephritis (GN) [22, 36]. Fourthly, neutralization of both ligands effectively blocked the development of mesangial proliferation in animal models [11, 34, 35, 37]. Finally, neutralization of both ligands reduced the progressive course and sequelae in progressive mesangioproliferative GN models [38–40] (Figure 3). The activation of mesangial cells towards a profibrotic (or ‘prosclerotic’) phenotype was also reduced in the above-mentioned interventional studies. Taken together, a large body of evidence supports the role of the PDGFR-β–PDGF-BB and -DD axis in mesangial cell proliferation and mesangial sclerosis.

We found no major differences in mesangial cells stimulated with PDGF-BB (ligand for both PDGFR-α and -β) versus PDGF-DD (PDGFR-β-specific ligand) [16]. Mesangial cells express PDGFR-α and are responsive to PDGF-CC in vitro. Furthermore, PDGF-CC is de novo expressed in podocytes in IgA nephropathy [20, 41]. However, in vivo, the PDGFR-α–PDGF-CC axis does not seem to play a role in mesangial proliferation [17]. Similarly, in nephrogenesis (see above) there is no indication that the PDGFR-α–PDGF-CC axis participates in the development of the mesangium [11].

The role of PDGF-AA remains unclear, but given the receptor binding that is similar to PDGF-CC, it likely has little to no relevant effect on mesangial proliferation in vivo.

In a cDNA screen of PDGF-BB-stimulated mesangial cells, we have identified the nephroblastoma overexpressed gene (NOV, CCN3) as an endogenous PDGF antagonist, limiting mesangial proliferation [42, 43]. CCN3 belongs to the CCN protein family (Cyr61/CTGF/NOV), which is a group of matricellular proteins regulating cell proliferation, migration and differentiation. After stimulation of mesangial cells with PDGF-BB and -DD, CCN3 was the most prominently down-regulated gene, and it diminished PDGF-induced mesangial proliferation [43]. In normal kidneys, the CCN3 expression pattern somewhat resembled that of PDGF, namely being expressed in podocytes, vascular smooth-muscle cells, cells of the medullary interstitium and in collecting ducts. A de novo mesangial expression was observed after induction of mesangioproliferative GN in rats [43]. Systemic overexpression of CCN3 significantly reduced mesangial proliferation and also had beneficial effects on long-term progression in mesangioproliferative GN [42]. Interestingly, CCN3 also exhibited proangiogenic effects in the early phase of mesangioproliferative GN [42]. Our data thus identified CCN3 as a potent endogenous inhibitor of PDGF-BB and -DD in mesangial cells and mesangial proliferation. The effects of CCN3 might not be limited to dampening the PDGF-driven effects. In vitro in mesangial cells, CCN3 was also shown to limit the profibrotic effects of CCN2 [connective tissue growth factor (CTGF)] [44]. Growth arrest-specific protein-1 might be another factor that acts as an endogenous inhibitor of mesangial cell proliferation and potentially constitutes another in vivo PDGF antagonist [45].

**Figure 3:** Inhibition of PDGF-DD in progressive mesangioproliferative glomerulonephritis (GN)–reduced glomerular and tubulointerstitial damage and fibrosis. Significantly reduced fibrosis was observed after treatment with PDGF-DD-neutralizing antibody, even when the treatment was initiated late in the course of the disease, i.e. with already established interstitial fibrosis. Pictures show immunohistochemistry for collagen type III, vimentin and α-smooth-muscle actin (α-SMA) in IgG-treated control animals (upper panels) versus anti-PDGF-DD-treated rats (lower panels) with progressive mesangioproliferative GN. Anti-PDGF-DD-treated animals had reduced deposition of extracellular matrix protein collagen type III, reduced tubular injury and expansion of interstitial (myo-)fibroblasts (vimentin, arrow points to tubular expression of vimentin) and reduced interstitial but also glomerular myofibroblasts as indicated by α-SMA staining (the glomeruli are outlined by dashed circles). Magnification ×100. Taken and modified from [38] with kind permission from Oxford University Press.
In a rat model of mesangiproliferative GN, serum PDGF-DD increased up to 1000-fold [35]. This prompted us to analyse serum levels of PDGF-DD in patients with mesangiproliferative (IgA) nephropathy. Compared with healthy controls and patients with various types of GN, serum PDGF-DD was specifically increased in patients with IgA nephropathy [46]. The increase was by far not as robust as in the animal model, and it is unlikely that serum PDGF-DD would become an effective diagnostic biomarker in IgA nephropathy. Still, increased PDGF-DD was also found in children with IgA nephropathy [47]. Taken together, elevated serum levels of PDGF-DD in IgA nephropathy might serve as a biomarker in IgA nephropathy that could potentially guide therapy.

Interestingly, none of the four analysed single-nucleotide polymorphisms of PDGF-BB showed an association with the severity of IgA nephropathy [48].

**Other glomerular diseases**

Increased expression of both PDGFR-β and PDGF-BB in cells of glomerular crescents was demonstrated previously in human renal biopsies [49, 50]. In rats with anti-GBM nephritis, both PDGFR-β and PDGF-BB were overexpressed in the crescents [51, 52]. The expression of PDGFR-α and of the other ligands in crescentic GN is yet unknown. There are some interventional studies that used non-specific inhibitors that also affect PDGF signalling in models of crescentic GN [53–55]. Both trapidil, and more recently also imatinib, ameliorated the course of the crescentic GN models, the latter most likely via reduced macrophage influx. These studies are promising but they could not distinguish to what extent the beneficial effects were mediated specifically via inhibition of PDGF signalling. This is, however, a general problem of studies using non-specific and multi-kinase inhibitors such as imatinib (see below).

Some data showed that the expression of both ‘classical’ PDGFs and PDGFRRs were increased in humans and animals with lupus nephritis [49, 56]. Two studies showed that treatment with imatinib reduced the severity of nephritis in animal models [57, 58]. It is not clear, whether these were direct effects on the kidney or whether imatinib acted primarily on the immune response. Interestingly, serum PDGF-DD was significantly reduced in patients with lupus nephritis compared with both healthy controls and patients with other glomerular diseases [46]. The importance of this finding remains completely unclear.

In a mouse model of mixed cryoglobulinaemia with associated membranoproliferative GN, the expression of PDGF-BB and PDGF-β was increased and imatinib treatment ameliorated the disease [59, 60].

Scarce or no data exist on the potential role of PDGFs in other glomerular diseases. For example, patients with membranous nephropathy expressed PDGF-CC de novo in podocytes [20].

Mesangial proliferation and activation is observed in all of the above-mentioned glomerular diseases. Whether PDGFs play a role in these glomerular diseases beyond their effects on mesangial cell proliferation remains unclear.

PDGF-CC was shown to be pro-angiogenic [61]. We have recently shown that PDGF-CC accelerated capillary healing in mesangiproliferative GN, and its inhibition aggravated renal injury in both rat mesangiproliferative GN and in a murine model of thrombotic microangiopathy [17]. These effects were VEGF-independent and were mediated by the direct effects on glomerular endothelial cells and by paracrine effects mediated via macrophages but also via mesangial cells. Although PDGF-CC or its inhibition did not alter mesangial cell proliferation, it altered the expression of pro-angiogenic factors by mesangial cells. Hence, PDGF-CC appears to be a novel angiogenic factor for the glomerular endothelium.

**Hypertensive and diabetic nephropathy**

PDGF seems to be involved in pulmonary hypertension by acting on vascular smooth-muscle cells and pulmonary vascular remodelling [62, 63]. Although many of the data were generated using imatinib, i.e. a non-specific tyrosine-kinase inhibitor (TKI), first clinical phase II and III trials suggested a prolonged efficacy of imatinib treatment in patients with severe pulmonary hypertension [63]. PDGFs may also play a role in systemic (arterial) hypertension [7]. In rats, PDGF-BB, but not PDGF-AA or -AB, exerted hypotensive effects mediated via nitric oxide (NO) [64]. In two different rat models with malignant hypertension imatinib reduced renal damage but had no effect on blood pressure [65, 66]. It was also shown that PDGF-AA inhibition reduced renal injury in spontaneously hypertensive stroke-prone rats without affecting the blood pressure [67]. Thus, PDGFs are essential factors involved in atherosclerosis, vessel remodelling and kidney damage in hypertension, whereas effects on systolic blood pressure itself seem to be limited [7].

PDGFs are also up-regulated in diabetic nephropathy [11, 68]. Imatinib and postnatal genetic deletion of PDGFR-β both reduced renal injury, in particular mesangial expansion, in different murine models of diabetic nephropathy [69, 70]. Recently, PDGF-α signalling was shown to be essential for maintenance of proliferation of insulin-producing pancreatic β-cells [71]; it is, therefore, possible that PDGFs might be involved in diabetic nephropathy and diabetes even beyond the role in mesangial expansion.

**Interstitial fibrosis**

Both PDGF receptors and all ligands are up-regulated in fibrosis [11, 20, 21, 23, 41]. A number of studies analysed the role of PDGF inhibition in progressive models of mesangiproliferative, crescentic or other glomerular diseases (see above). Some studies initiated the treatment late after induction of the disease, i.e. at a time when glomerular disease had progressed to tubulointerstitial injury [38]. However, none of these studies could clearly distinguish between effects of PDGF inhibition in glomeruli versus the tubulointerstitium.

Few experimental studies have addressed the role of PDGF in models of tubulointerstitial fibrosis. One week of high-dose PDGF-BB injections induced proliferation of interstitial fibroblasts and their differentiation to myofibroblasts and fibrosis, but also apoptosis of these cells was observed [72]. Interestingly, PDGF-AA injections had no such effects [72]. However,
no such effects were observed during adenoviral hepatic over-
expression or infusion of PDGF-BB [22, 73]. At least in vitro
PDGF-DD acted as a mitogen for renal fibroblasts [38].

As for many other diseases, the role of PDGF-AA in tubu-
lointerstitial fibrosis remains unknown. However, mice with a
PDGFR-α-activating mutation developed widespread fibrosis
in various organs including the kidneys [74]. We showed that
both genetic PDGF-C deficiency and neutralizing antibodies
to PDGF-CC significantly blunted the development of fibrosis
in murine obstructive nephropathy [24]. This effect seems to
be kidney specific, since we found no such effects in models of
liver fibrosis [75]. At first glance, the profibrotic role of PDGF-
CC appears inconsistent with its pro-angiogenic activity, since
there is considerable evidence that the loss of peritubular cap-
illaries accompanies renal fibrosis and that pro-angiogenic
factors, such as VEGF-121, can rescue progressive interstitial
fibrosis [76]. Therefore, our own ongoing studies will attempt
to assess the relative importance of both processes in renal
fibrosis.

One elegant study showed that PDGFR-α- and β-neutral-
izing antibodies as well as imatinib ameliorated ischaemia and
obstruction-induced tubulo-interstitial fibrosis in mice; combi-
nation treatment with both antibodies was not additive [21].
Another recent study identified Dickkopf-related protein 1
(Dkk-1), an inhibitor of the WNT/β-catenin signalling pathway,
as a significant inhibitor of PDGF-BB-induced proliferation
of renal pericytes or perivascular fibroblasts in vitro. Dkk-1 was
antifibrotic in models of interstitial fibrosis, and also antago-
nized profibrotic effects of CTGF and TGF-β [77]. Suramin, a
non-specific inhibitor of several growth factors including
PDGFs, also inhibited renal fibrosis in various models of renal
fibrosis [78, 79]. But as with other such molecules it remains
unclear to what extent these effects were mediated via PDGF.

Taken together, there is mounting evidence that antagon-
ism of PDGFs, in particular PDGF-CC and PDGFR-α, may
represent attractive antifibrotic targets.

Acute kidney injury

To date, only one study has suggested a potential renal
side-effect of PDGF inhibition. Treatment with either the non-
specific anti-platelet agent trapidil or a multi-kinase inhibitor
aggravated renal damage in a model of acute kidney injury
[80]. It is unclear whether these effects were indeed mediated
by inhibition of PDGFs. Tubular cells do not express PDGFRs
which might rather argue against such effects. Indeed, imatinib
or neutralizing antibodies to both PDGFRs reduced renal
fibrosis in a mouse model of ischaemia-reperfusion injury [21].
However, formal studies are required to exclude that PDGF
antagonism interferes with renal recovery in acute kidney injury.

Translation to the clinic

Two clinical phase I studies showed that PDGF-DD neutral-
izing antibody in healthy subjects [81] or a highly specific
PDGFR TKI in patients with advanced solid tumours were
well tolerated [82]. A PDGFR-β antibody fragment resulted in
increased fluid retention in a small study of patients with ad-
vanced ovarian or colorectal cancer [83]. To date, no other
clinical studies with specific PDGF inhibitors, like antibodies,
soluble receptors or aptamers, have been published. Consider-
ing the data available on TKIs such as imatinib, PDGF-related
side-effects could involve defective wound-healing, myelosup-
pression, fluid retention and cardiovascular and bone toxicity
[83–86]. Several pharmaceutical companies have developed or
are developing specific PDGF/PDGFR inhibitors mainly for
cancer indications [21, 87].

There are a number of established and clinically used TKIs
that (also) target PDGFRs, one prototype being imatinib. Ima-
tinib was developed as an inhibitor of the c-abl kinase and is
being used successfully for the treatment of chronic myeloic
leukaemia. Imatinib is, as the majority of the currently used
TKIs, rather non-specific, and inhibits c-kit, PDGFR and
c-fms tyrosine kinases. Experimental studies have shown the
renoprotective role of imatinib in various models of renal
diseases (see above). However, in general it remains unclear to
what extent the observed effects can be attributed to the inhibi-
tion of PDGF tyrosine kinase and to what extent these
effects might rather argue against such effects [9, 88]. However,
the treatment of most renal diseases will require a long-term application
which might be hampered by the side-effects of imatinib or similar TKIs (see above). For example, a high number of adverse effects including a new onset of proteinuria were rec-
corded in a phase I/IIa study of 1-year treatment with imatinib
in patients with systemic sclerosis-associated interstitial lung
disease [89]. This suggests that more targeted therapeutic
approaches may be necessary.

CONCLUSIONS

The major and best described functions of PDGFs, in particu-
lar of PDGF-β/PDGF-BB and -DD, are their mitogenic role
for mesangial cells. The role of PDGF in mesangial activation
towards a profibrotic phenotype, i.e. in mesangial sclerosis,
was suggested by several interventional studies, but is less well
established. Mesangial hypercellularity and sclerosis are found
in many glomerular diseases including IgA nephropathy,
lupus, diabetes, membranoproliferative GN and hypertension.
This can on the one hand explain the renoprotective effects of
PDGF inhibition in these diseases (although mostly shown for
imatinib), and on the other hand this supports a possible broad clinical applicability of PDGF inhibition. Whether
PDGF inhibition has specific effects in glomerular diseases
beyond the effects on mesangial cell proliferation and activi-
tion remains unclear. PDGFR-α/PDGF-AAA and -CC seem
to play a role in glomerular capillary healing and angiogenesis
and thus lend themselves to studies in thrombotic microangi-
pathy and other renal conditions characterized by widespread
endothelial damage.

The other major role of PDGFs seems to be a profibrotic
action and thus, PDGF antagonism may become a target in
any progressive CKD. Both PDGF receptors -α and -β seem
to be involved in proliferation and activation of interstitial fibro-
blasts. Surprisingly, however, this is far less well described
compared with the role of PDGF in mesangial proliferation.
Apart from PDGF-CC, PDGF-specific intervention studies in
renal fibrosis are missing. Clarification of the role of PDGFs in
ischaemia-reperfusion injury and tubular regeneration des-
erves further studies. Clinical trials are feasible, since various
tools to manipulate PDGF signalling have been or are being
developed.

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CONFLICT OF INTEREST STATEMENT

None declared.

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TWEAK and the progression of renal disease: clinical translation

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ABSTRACT

Tumour necrosis factor-like weak inducer of apoptosis (TWEAK) activates the fibroblast growth factor-inducible-14 (Fn14) receptor. TWEAK has actions on intrinsic kidney cells and on inflammatory cells of potential pathophysiological relevance. The effects of TWEAK in tubular cells have been explored in most detail. In cultured murine tubular cells TWEAK induces the expression of inflammatory cytokines, downregulates the expression of Klotho, is mitogenic, and in the presence of sensitizing agents promotes apoptosis. Similar actions were observed on glomerular mesangial cells. In vivo TWEAK actions on healthy kidneys mimic cell culture observations.

Increased expression of TWEAK and Fn14 was reported in human and experimental acute and chronic kidney injury. The role of TWEAK/Fn14 in kidney injury has been demonstrated in non-inflammatory compensatory renal growth, acute kidney injury and chronic kidney disease of immune and non-immune origin, including hyperlipidaemic nephropathy, lupus nephritis (LN) and anti-GBM nephritis. The nephroprotective effect of TWEAK or Fn14 targeting in immune-mediated kidney injury is the result of protection from TWEAK-induced injury of renal intrinsic cells, not from interference with the immune response.

A phase I dose-ranging clinical trial demonstrated the safety of anti-TWEAK antibodies in humans. A phase II randomized placebo-controlled clinical trial exploring the efficacy, safety and tolerability of neutralizing anti-TWEAK antibodies as a tissue protection strategy in LN is ongoing. The eventual success of this trial may expand the range of kidney diseases in which TWEAK targeting should be explored.

Keywords: apoptosis, clinical trials, fibrosis, inflammation, necroptosis, proteinuria

INTRODUCTION

Tumour necrosis factor-like weak inducer of apoptosis [TWEAK, Apo3L, tumour necrosis factor superfamily (TNFSF)12] is a cytokine that belongs to the TNFSF that activates Fibroblast growth factor-inducible-14 (Fn14, TWEAK receptor, TNFRSF12A, CD266), a TNF receptor superfamily (TNFRSF) protein [1–4]. In recent years, evidence has accumulated supporting a role for TWEAK activation of intrinsic renal cell Fn14 receptors in the pathogenesis of acute and chronic kidney injury, glomerular and tubulointerstitial damage and non-immune and