The Growth Factors: Potential Biomarkers and Therapeutic Targets in Kidney Diseases

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Abstract
Background: Kidney diseases are a prevalent health problem worldwide. Although substantial progress has been made in understanding the pathophysiology of kidney disease, currently there is no satisfactory clinical treatment available to prevent or treat kidney disease. Therefore, strategies to establish early diagnosis, identify the key molecules, and develop novel therapeutic interventions to slow the progression of kidney diseases and reduce their complications are encouraged. Summary: The growth factors play a crucial role in the development of kidney diseases. The altered levels of growth factors are usually detected in circulation and urine in the disease course. A growing body of studies has suggested that growth factors, receptors, and related regulators are promising biomarkers for the diagnosis and/or prognosis and potential therapeutic targets for the treatment of kidney diseases. In this review, we summarize recent advances in the potential applications of growth factors for diagnostic biomarkers and therapeutic targets in kidney diseases and highlight their performances in clinical trials. Key Messages: Most diagnostic and therapeutic strategies targeting growth factors are still far from clinical implementation. The better understanding of growth factor-regulated pathophysiology and the progress of new intervention approaches are expected to facilitate the clinical translation of growth factor-based diagnosis and therapy of kidney diseases.

Introduction

Kidney diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD), have become a global public health concern associated with high morbidity, mortality, and healthcare costs. AKI is defined by a rapid increase in serum creatinine, decrease in urine output, or both. Renal ischemia/reperfusion injury (IRI), infections, shock, sepsis, and drugs are the major risk factors for developing AKI and subsequent CKD. Although substantial progress has been made in understanding the pathophysiology of kidney disease, the molecular mechanisms contributing to kidney injury remain largely unclear. Mean-
while, currently there is no satisfactory clinical treatment available to prevent or treat kidney disease because of the poor therapeutic efficacy and systemic side effects. Therefore, strategies to establish early diagnosis, identify the key molecules, and develop novel therapeutic interventions to slow the progression of kidney diseases and reduce their complications are encouraged.

The growth factors are a subset of cytokines stimulating the growth of specific tissues [1]. Secreted growth factors bind to specific cell-surface growth factor receptors to stimulate, or in some cases, inhibit cell proliferation and differentiation processes, and play important roles in inflammatory responses and tissue repair. The growth factors not only participate in the progression of diseases but also are used for the treatment of diseases such as the hematopoietic growth factors (HGFs), and erythropoietin has been used for anemia [2].

The role of kidney-produced growth factors has been widely investigated in maintaining kidney physiological functions and in the pathogenesis of kidney diseases (Fig. 1). The potential of growth factors, receptors, and related regulators as diagnostic markers and therapeutic targets of kidney diseases has attracted extensive attention for decades and is still ongoing [3]. Therefore, the current review mainly focuses on summarizing recent findings of kidney-produced growth factors for their application potential as biomarkers to predict renal diseases and evaluating the current growth factor-targeted therapy or diagnosis in clinical trials.

**Transforming Growth Factor Beta (TGF-β) Superfamily**

The transforming growth factor beta (TGF-β) superfamily consists of more than 30 members including TGF-β, bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), activins (ACTs), inhibins (INHs), glial-derived neurotrophic factors (GDNFs), Müllerian inhibiting substance (MIS), left-right determination factor (Lefty), and nodal growth differentiation factor (Nodal). Although TGF-β is widely accepted as a key mediator of renal fibrosis, clinical studies of anti-TGF-β antibodies fesolimumab and LY2382770 in focal segmental glomerulosclerosis (FSGS) and diabetic kidney disease (DKD) have failed in phase 2 trials owing to a lack of beneficial effect on renal damage [4, 5]. In addition to the profibrotic actions, TGF-β also plays multiple physiological roles such as cell proliferation, apoptosis, differentiation, autophagy, and immune responses [6]. The failure of clinical studies of TGF-β blockade may relate to the possible adverse effects, such as autoimmu-
nity, hyperinflammation, and increased tumorigenesis [7]. In this review, we summarize recent advances highlighting the role of other members of TGF-β superfamily in kidney diseases.

**Bone Morphogenetic Proteins**

Bone morphogenetic proteins (BMPs), members of the TGF-β superfamily, play essential roles in multiple key steps of embryonic development, and after birth in the pathophysiology of several diseases, including various kidney diseases. Among BMPs, BMP7 is considered a potent antagonist to TGF-β1 and the most prominent member involved in renal development and disease. BMP7 has attracted much attention because of its protective role in AKI and CKD [3, 8]. Kidney BMP7 is reduced in different pathological conditions such as renal IRI, tubulointerstitial fibrosis, DKD, and hypertensive nephrosclerosis and increased again during the regenerative phase [9, 10]. Importantly, data from the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial cohorts have demonstrated the negative association of circulating BMP7 with

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**Fig. 2.** Therapeutic agents targeting BMP7, HGF, and CTGF for kidney diseases in clinical trials. The BMP7-derived small peptide THR-184 is an agonist of BMP7 receptor ALK3 and has been tested for the prevention of cardiac surgery-associated acute kidney injury (CSA-AKI). ANG-3777, a HGF mimic, can selectively activate the HGF/c-Met pathway, thereby contributes to the repair of damaged tissues. ANG-3777 is in clinical trials for AKI associated with delayed graft function (DGF) and cardiac surgical procedures involving cardiopulmonary bypass (CPB). FG-3019 is a human anti-CTGF monoclonal antibody inhibiting the activity of CTGF and has been used in clinical trials for the treatment of DKD with microalbuminuria. FG-3019 may inhibit the binding of CTGF to growth factors, matrix proteins, integrins, and receptors such as EGFR.
kidney outcome in patients with type 2 diabetes (T2D) and further identified BMP7 as a useful biomarker for predicting progressive kidney disease [11].

The beneficial effects of BMP7 in kidney diseases have been extensively studied. Administration of recombinant or transgenic overexpression of BMP7 ameliorates kidney injury in AKI, obstructive and diabetic injuries, and lupus nephritis in animal models via suppressing inflammation, apoptosis, epithelial-to-mesenchymal transition, and reversing fibrosis [3, 10, 12]. Currently, peptide-based agonists for BMP7 signaling have been developed [12]. THR-123 and THR-184, produced by Thrasos Therapeutics are agonists of the activin-like kinase-3 receptor (ALK3), the main BMP7 receptor in tubular epithelial cells (TECs) [12]. THR-184 has been tested in a phase 2 clinical trial for the prevention of cardiac surgery-associated AKI (Fig. 2) [13, 14]. Although Thrasos Therapeutics stated that there was a reduction in the extent of AKI within 7 days of surgery in patients with CKD treated with the highest dose of THR-184 [15], the results originating from that trial showed that THR-184 at a range of doses failed to reduce the incidence, severity, or duration of AKI after cardiac surgery in high-risk patients [16].

**Growth Differentiation Factors**

Growth differentiation factors (GDFs) are a subfamily of growth factors belonging to TGF-β superfamily. Among them, GDF15 is associated with multiple diseases, such as cancer, cardiovascular disease, metabolic disease, and kidney disease [17]. In preclinical studies of kidney injury, kidney GDF15 expression is increased and appears to play a protective role [18]. GDF15-deficient diabetic mice show glycosuria, polyuria, more severe fibrosis, substantially more tubular damage, but no differences in glomerular injury [19]. In unilateral ureteral obstruction (UUO) mice model, recombinant GDF15 treatment displays a beneficial role by reducing renal fibrosis and fibroblast activation [20]. In addition, deficiency of GDF15 exacerbates acute tubular injury and enhances inflammatory responses in mice with renal IRI [21]. A recent study supports that GDF15 is induced in a compensatory manner during AKI and CKD, which is insufficient to fully prevent kidney injury, but further increments in GDF15 are nephoprotective [22].

In clinical studies, the levels of serum GDF15 are positively correlated with the risk of AKI in patients undergoing cardiac bypass surgery or percutaneous coronary interventions [18]. In a prospective case-control study, GDF15 is identified as a clinically valuable marker for predicting transition in albuminuria stage in both T2D and nondiabetic hypertension patients [23]. In a multiple regression analysis of T2D patients with DKD, GDF15 is an independent predictor of renal events, but not of cardiovascular events [24]. In type 1 diabetes patients with DKD, higher plasma GDF15 is a predictor of all-cause and cardiovascular mortality and is associated with a rapid decline in kidney function [25]. Additionally, urinary GDF15 levels in patients with CKD or T2D with decreased glomerular filtration rate (GFR) are increased and associated with kidney tubular injury and mortality [18, 26]. Collectively, these findings indicate that GDF15 may be a potential candidate for the treatment of kidney diseases.

**Inhibins and Activins**

Inhibins and activins are originally identified based on their ability to inhibit and stimulate pituitary follicle-stimulating hormone (FSH), respectively. Inhibins are heterodimers made up of a subunit and either a βA subunit (αβA, inhibin A) or a βB subunit (αβB, inhibin B), whereas activins are homo- or heterodimers of the βA and βB subunits (βAβA, activin A; βBβB, activin B; and βAβB, activin AB). Among inhibins and activins, activin A and B have been reported to be involved in the pathophysiologic mechanism of various kidney diseases [27].

Activin A is secreted and initiates related signaling pathways by binding to a type 2 receptor, ActRIIA or ActRIIB [28]. Activin A affects renal cells, such as renal interstitial fibroblasts, tubular and mesangial cells and promotes fibrosis directly or through mediating TGF-β1 responses [29, 30]. The expression of renal activin A is upregulated in cortical and medullary tubular cells, or interstitial fibroblasts in rat UUO model [29, 31]. In rats with anti-Thy1 glomerulonephritis, activin A overexpression is linked to fibrosis [32]. Increased circulating and renal activin A are also observed in particular 5/6 nephrectomy ldlr knockout mice fed a high-fat diet and Alport (Col4a5 deficient) mice [33, 34]. Both tubular epithelial and glomerular cells-localized activin A are upregulated in diabetic mice and human with DKD [30, 35, 36]. Interestingly, the expression of follistatin, an endogenous negative regulator of activins, is downregulated in the kidney under diabetic conditions [36].

Recently, activin B has been identified to play an important role in the pathogenesis of CKD [37]. It is found that activin B is induced mainly in TECs from various mouse models of renal fibrosis including UUO, renal IRI, and DKD, which is further confirmed in the kidney from patients with CKD. The mechanism study indicates that the induction of activin B in injury TECs is mediated by

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transcriptional factor Sox9. Subsequently, TECs-derived activin B contributes to renal fibrosis by activating the interstitial fibroblasts through activin B/Smad signaling [37].

**Epidermal Growth Factors**

Preclinical studies have shown that the epidermal growth factor receptor (EGFR) is a potential therapeutic target for kidney diseases. Deletion of EGFR in proximal tubules impairs the regeneration of TECs in mice subjected to renal IRI [38]. The most prominent ligands of EGFR are epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF) and TGF-α. Among them, EGF is the most widely studied and has the highest affinity for EGFR. EGF is highly expressed in adult kidney and acts as a proproliferative protein that mediates kidney tubular cell differentiation, repair, and regeneration [39]. Decreased urinary EGF is found in patients with a variety of kidney diseases including AKI, DKD, IgA nephropathy, and ureteropelvic junction obstruction [40]. According to recent studies, lower urinary EGF and higher urinary monocyte chemoattractant protein-1 (MCP-1) are associated with severer interstitial fibrosis and tubular atrophy [39, 41]. Both lower urinary EGF and higher MCP-1 are significantly associated with greater progression of DKD [42, 43], and a lower EGF/MCP-1 ratio predicts kidney function decline in various glomerular diseases [41, 44]. Furthermore, urinary EGF and MCP-1 are each independently associated with CKD outcome after cardiac surgery [45]. Importantly, lower urinary EGF is associated with increased risk of rapid GFR loss and incident CKD in the general population [46]. Taken together, the urinary EGF may serve as a broadly applicable biomarker representing the tubular component of the current glomerulus-centric clinical risk assessment system [46].

**Fibroblast Growth Factors**

Fibroblast growth factors (FGFs) are pleiotropic proteins involving in a wide range of biological and pathological functions by regulating cell differentiation, proliferation, migration and survival. Twenty-two FGF ligands and five FGF receptors (FGFRs) including FGFR1-4 and FGFR1L have been identified. FGF/FGFR plays a significant role in kidney development and in the pathogenesis of kidney diseases [47]. In recent years, endocrine FGF21 and FGF23 have attracted extensive attention in the field of kidney diseases. Elevated circulating FGF21 levels have been reported in dyslipidemia, insulin resistance, the metabolic syndrome, T2D, nonalcoholic fatty liver disease, atherosclerosis, and coronary artery disease [48], all of them are the major risk factors for CKD progression. Importantly, the increased levels of serum FGF21 are detected in patients with stage 2 CKD, and the serum FGF21 concentration increases gradually with the progression of CKD from early stage to end stage [47, 48]. A series of studies have concluded that serum FGF21 levels are negatively associated with renal function [49]. It has been reported that FGF21 directly suppresses renal lipid accumulation; protects against renal fibrosis, inflammation, and oxidative stress [48], suggesting that FGF21 is a potential biomarker or therapeutic agent for CKD. The FGF21 analogue, LY2405319 has been developed and tested through phase 1 clinical trial to reduce body weight and fasting insulin and improve dyslipidemia in patients with T2D and obesity [50].

FGF23 is secreted from bone tissue and binds to a complex of α-Klotho and FGFR1c, FGFR3c, or FGFR4 and regulates systemic phosphate homeostasis and vitamin D metabolism. Dietary phosphate loading, hypercalcemia, parathyroid hormone, and 1,25-dihydroxyvitamin D stimulate FGF23 production from the bone tissue. Meanwhile, FGF23 induces urinary phosphate excretion and inhibits the synthesis of 1,25-dihydroxyvitamin D in the kidney and reduces parathyroid hormone biosynthesis in the parathyroid gland. The recent studies of FGF23 have expanded the understanding of the pathophysiology of mineral metabolic disorders in CKD. In patients and animals with CKD, plasma FGF23 levels are early increased before other alterations in mineral metabolism, indicating FGF23 excess is critical to maintaining normal circulating phosphate in CKD and the main cause of subsequent 1,25-dihydroxyvitamin D deficiency and secondary hyperparathyroidism. Decreased expression of Klotho in renal tissue observed in the early stages of CKD has been considered a possible primary upstream factor that drives FGF23 excess because extremely elevated plasma FGF23 is observed in primary Klotho deficiency. However, this hypothesis is still controversial, and impaired FGF23 cleavage is an alternative mechanism [51]. In addition, the elevated circulating FGF23 levels can be used as a biomarker for the diagnosis and/or prognosis of CKD [47, 52, 53] and are associated with increased mortality, cerebrovascular events, atrial fibrillation, left ventricular hypertrophy, and heart failure in CKD [51].
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Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) is originally isolated as a mitogen that can stimulate hepatocyte proliferation [3]. Subsequent studies have found that HGF can bind to c-met receptor expressing in the epithelial cells and acts on a variety of cells through an autocrine or paracrine manner [55]. The role of HGF-c-met axis is closely related to embryonic development, angiogenesis, tissue repair, and cancer. In the kidney, HGF is mainly secreted by epithelial cells, mesangial cells, endothelial cells, and macrophages, and c-met receptors locate on fibroblast, peritubular endothelial cells [3, 12]. Later, a novel family of VEGF-A isoforms arising from an alternative 3’ splice-site in the terminal exon 8 is termed VEGF-Axxxb [62]. There is strong evidence suggesting that both VEGF-A expression and splicing are critical regulators of renal function [61, 62].

Both podocyte-specific VEGF-A depletion and VEGF-A overexpression in mice have been shown to result in CKD [63]. VEGF-A inhibitors and VEGFR-2 inhibitors are commonly used in antiangiogenic therapy of cancer, but these agents often cause side effects leading to renal damage [64]. A decreased renal expression of VEGF-A has been found to correlate with the GFR of patients with CKD [65, 66]. Meanwhile, elevated circulating and urinary VEGF-A levels are found in patients with crescentic glomerulonephritis (CrGN) and DKD [67, 68]. On the other hand, patients in the early stages of DKD with relatively normal kidney function express a higher level of the

ANG-3777, produced by Angion Biomedica Corporation, is a small molecule with HGF-like activity [57]. In a phase 2 study in renal transplantation patients showing signs of delayed graft function, there is an efficacy signal for improved renal function in subjects treated with ANG-3777, with a good safety profile [58]. Therefore, a phase 3 trial of ANG-3777 in renal transplant recipients with delayed graft function has been designed [59]. Additionally, a multicenter phase 2 study to evaluate the safety and efficacy of ANG-3777 in preventing AKI following cardiac surgical procedures involving cardiopulmonary bypass is also underway (Fig. 2) [60].

Vascular Endothelial Growth Factors

The vascular endothelial growth factor (VEGF) family includes several members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E (viral VEGF), VEGF-F (snake venom VEGF), placental growth factor (PGF), and endocrine gland-derived vascular endothelial growth factor (EG-VEGF). VEGF-A is a well-studied member of the VEGF family by binding VEGF receptor (VEGFR)-1 and VEGFR-2 and regulates angiogenesis. In the glomerulus, VEGF-A secreted by mature podocytes binds to VEGFRs on the glomerular endothelial cell (GEnC) and further promotes GEnC proliferation, migration, and survival. In human kidney, VEGF-A is also expressed in renal tubules, and VEGFR-1 and VEGFR-2 are expressed on GEnC and peri-tubular endothelial cells [61]. It is noteworthy that multiple isoforms of VEGF-A ranging from 121 to 206 amino acids can be generated through alternative exon splicing, and VEGF-A165 is the most predominant. Later, a novel family of VEGF-A isoforms arising from an alternative 3’ splice-site in the terminal exon 8 is termed VEGF-Axxxb [62]. There is strong evidence suggesting that both VEGF-A expression and splicing are critical regulators of renal function [61, 62].

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VEGF-A<sub>165b</sub> isoform relative to VEGF-A<sub>165</sub>. However, during the later stages of DKD, when estimated GFR has declined, the increased expression of VEGF-A<sub>165b</sub> is diminished [69]. Podocyte-specific overexpression of VEGF-A<sub>165b</sub> in the kidney rescues endothelial dysfunction in renal disease, suggesting the modulation of VEGF-A splicing is a potential therapeutic avenue [61]. In fact, many growth factors and growth factor receptors also have splice variants and have been implicated in kidney diseases [62].

Other VEGFs are also involved in kidney diseases. Higher serum VEGF-C level has been identified as a potential new biomarker of volume status in patients with CKD [70], and higher serum VEGF-B and VEGF-D levels are correlated with renal dysfunction in patients with DKD [71, 72]. VEGF-C and VEGF-D are also involved in lymphangiogenesis in renal fibrosis, and the blockade of VEGF-C and VEGF-D signaling decreases obstruction-induced lymphangiogenesis [73]. These studies offer a potential novel therapeutic approach to kidney diseases by targeting VEGF-B, VEGF-C, and VEGF-D. For instance, PGF is a ligand of VEGFR-1, which is often used as a biomarker of cardiovascular events. Plasma PGF, GDF15, and FGFR23 are significantly associated with estimated GFR decline per year in the replication cohort from the Uppsala Longitudinal Study of Adult Men (ULSAM), and these growth factors can be used to predict CKD incidence [74]. More recently, PGF is identified as one of the top performing circulating plasma biomarkers for kidney disease progression in a prospective cohort study of 549 individuals with biopsy-confirmed kidney diseases by using a proteomics assay [75]. Another study in 1,444 adults undergoing cardiac surgery demonstrates that higher postoperative PGF levels are independently associated with lower odds of AKI, long AKI duration, and mortality [76].

**IGF System**

The insulin-like growth factor (IGF) system includes IGF-1 and IGF-2, type I and type II receptors (IGF-RI and IGF-RII), high-affinity IGF-binding proteins (IGFBPs), low-affinity IGFBP-related proteins (IGBP-rPs), and IGFBP proteases. IGF-1 mediates many growth hormone actions. The IGF system is essential to the maintenance of normal renal function, and the dysregulation of IGFs has been implicated in a range of kidney diseases [77, 78]. However, the function of IGF in kidney diseases is still controversial. IGF activity is increased in early DKD, whereas decreased IGF activity contributes to the morbidity related to CKD, indicating that the IGF system must be finely balanced for optimal renal outcomes [78]. In CKD, evidence obtained from rodent models and humans has shown that the growth hormone/IGF-1/IGFBPs axis is involved in the pathogenesis of DKD, and IGF-1 plays an important role in the early development of DKD [79, 80]. In AKI, the reduced serum IGF-1 levels are correlated with the increased mortality and the nutritional status of AKI patients. Therefore, serum IGF-1 is a suitable candidate as an early and sensitive biomarker for AKI mortality in the ICU [3]. Although IGF-1 is shown to be therapeutic potential in rodent models of AKI, this is not the case in human AKI [3]. In recent years, the role of IGFBPs in kidney diseases has been paid much attention [81]. Among them, IGFBP-7 is highly expressed in renal tubules and is mainly used as the early predictive and prognostic marker for AKI [81]. The urine compound of tissue inhibitor of metalloproteinase-2 (TIMP-2) and IGFBP-7 has been approved by US Food and Drug Administration (FDA) as the first biomarker for risk assessment of AKI in ICU patients in 2014 [81].

IGFBP-rP2, also named as connective tissue growth factor (CTGF) or CCN2, is widely expressed in the kidney. CTGF is well studied because it is a direct mediator of TGF-β-induced fibrosis. At present, no specific CTGF receptor has been identified. CTGF may exert its effects through binding various molecules, including growth factors, matrix proteins such as fibronectin and proteoglycans, and cell surface molecules such as integrins, some receptors [7]. In the kidney, CTGF is upregulated in patients with DKD, chronic allograft nephropathy, hypertensive nephrosclerosis, and CrGN [7]. The plasma and urinary CTGF level is elevated in a variety of CKD and acts as an independent predictor for end-stage renal disease [82]. Despite FG-3019, an anti-CTGF antibody showed well tolerated and led to a reduction of microalbuminuria in two phase 1 trials in DKD (Fig. 2); the following clinical trials in subjects with FSGS and DKD are prematurely stopped [5].

**Platelet-Derived Growth Factors**

Platelet-derived growth factor (PDGF) is critically involved in the progression of kidney diseases, especially those characterized by mesangial cell proliferation and interstitial fibrosis [4]. Currently, among four PDGF isoforms and two PDGF receptor (PDGFR) subunits, five different PDGF dimers (PDGF-AA, PDGF-BB, PDGF-
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CC, PDGF-DD, and PDGF-AB) and three PDGFR dimers (PDGFR-αα, PDGFR-ββ, and PDGFR-αβ) are formed, respectively. In the kidney, PDGF is produced by different cell types, including podocytes and TECs. PDGFs bind to the dimerized PDGFRs expressed on mesenchymal cells in the kidney and promote the proliferation and/or recruitment of fibroblasts, mesangial cells, pericytes, and smooth muscle cells [4, 7]. Increased expression of components of the PDGF system has been observed in the kidney from a wide variety of renal diseases, such as mesangial proliferative glomerulopathy, IgA nephropathy, CrGN, lupus nephritis, membranous nephropathy, and transplant glomerulopathy [4, 7, 83]. The circulating PDGF-D is elevated in patients with IgA nephropathy, and urinary excretion of PDGF-A and PDGF-AB/PDGFB is also increased in patients with uncomplicated type 1 diabetes [7].

Many preclinical studies have shown that the antagonism of PDGF/PDGFR signaling can ameliorate kidney diseases of diverse etiologies. In anti-Thy1 glomerulonephritis rat model, treatment with PDGFR/Fc chimeric molecule, oligonucleotide aptamer antagonist against PDGF-B, or PDGF-D-neutralizing antibody can effectively reduce mesangial proliferation and prevent the subsequent development of renal fibrosis [4, 7, 84]. PDGF-D deficiency results in a reduction in renal interstitial fibrosis in UUO and unilateral IRI models [4]. Both anti-PDGF-C IgG and PDGF-C deficiency effectively reduce kidney fibrosis in UUO model [7]. In addition, PDGFR kinase inhibitors, such as imatinib and AG1295, reduce renal fibrosis in models of autoimmune nephritis, DKD, hypertension, chronic allograft nephropathy [4]. PDGFR-β deficiency improves the glomerular and interstitial morphology in experimental DKD [85]. These studies suggest that PDGF system may represent therapeutic targets for kidney diseases. However, this strategy still lacks the implementation of clinical studies.

**Progranulin**

As an autocrine growth factor, progranulin (PGRN) has multiple physiological functions and is widely involved in the pathogenesis of many types of diseases such as autoimmune disorders, atherosclerosis, and cancer. PGRN is also an important anti-inflammation molecule by mainly targeting the proinflammatory signaling of TNFα. Our studies found that level of PGRN is significantly reduced in the kidney in a mouse model of renal IRI [86]. PGRN deficiency in mice significantly aggravates renal injury as evidenced by higher serum creatinine, more severe morphological injury, and inflammatory responses [86]. Importantly, recombinant human PGRN has a therapeutic potential for the treatment of AKI [86]. Accumulating evidence has shown that nucleotide oligomerization domain (NOD)-like receptors (NLRs) are highly involved in the pathogenesis of kidney diseases [87]. Our studies further indicate that PGRN, at least in part, negatively regulates the inflammatory responses mediated by NOD2, a member of NLRs [86]. In the following studies, we found that the PGRN expression in the kidney is decreased in diabetic mice and patients with biopsy-proven DKD [88]. PGRN deficiency results in exacerbated podocyte injury, whereas recombinant human PGRN administration effectively ameliorates renal injuries in diabetic mice [88]. Mechanistically, PGRN maintains mitochondrial homeostasis via Sirt1-PGC-1α/AMPK pathway, thus protecting podocytes under diabetic conditions [88, 89]. The decreased renal PGRN has also been confirmed in CKD mice [90]. Interestingly, the circulating PGRN is increased in human and animal models of AKI and CKD, indicating that increased circulating PGRN may be a compensatory mechanism to limit renal dysfunction [90].

**Myeloid-Derived Growth Factor**

Myeloid-derived growth factor (MYDGF), originally identified as a paracrine protein secreted by bone marrow-derived monocytes and macrophages [91]. Studies have demonstrated that MYDGF plays a protective role in cardiovascular system. MYDGF mediates heart repair after myocardial infarction [91, 92], promotes cardiomyocyte proliferation and improves heart regeneration in mice after cardiac injury [93], inhibits endothelial damage and atherosclerosis in apolipoprotein E knockout mice [94], and protects against pressure overload-induced heart failure [95]. Recent studies have found that MYDGF is also involved in the pathogenesis of kidney diseases. The plasma levels of MYDGF are reduced in diabetic mice and patients [96]. MYDGF not only improves glucose/lipid metabolism in diabetic mice but also alleviates podocyte injury DKD [96, 97]. By generation of bone marrow-derived MYDGF in maintaining glucose metabolism and renal function under diabetic condition has been addressed [97]. Recently, our study found that MYDGF is also ex-
Table 1. Summary of growth factors as biomarkers for the diagnosis of kidney diseases in the present review

| Growth factor | Level | Population | Clinical association and usefulness | Reference |
|---------------|-------|------------|-------------------------------------|-----------|
| BMP7          | Circulating level ↓ | T2D mellitus | Predictor of renal end points in T2D patients | [11] |
| GDF15         | Circulating level ↑ | Cardiac bypass surgery and percutaneous coronary interventions CKD DKD | Positively correlated with the risk of AKI Associated with an increased risk of CKD progression Predictor of the rapid decline of kidney function in DKD Predictor of all-cause and cardiovascular mortality in T1D patients with DKD | [18, 23–26] |
|               | Urinary level ↑ | CKD T2D with decreased GFR | Associated with kidney tubular injury and mortality | |
| EGF           | Urinary level ↓ | AKI, DKD, IgA nephropathy, UPJO | A broadly applicable biomarker representing the tubular component of the current glomerulus-centric clinical risk assessment system | [39–46] |
| FGF21         | Circulating level ↑ | CKD | Negatively associated with kidney function | [47–49] |
| FGF23         | Circulating level ↑ | CKD | Biomarker for the diagnosis and prognosis Associated with increased mortality, cardiovascular and cerebrovascular events | [3, 47, 51–53] |
|               | Circulating level ↑ | AKI | Early prognostic marker Candidate prognostic marker for adverse outcomes | |
| HGF           | Urinary level ↓ | AKI, RRT | Associated with an increased probability of renal recovery | [56] |
| VEGF-A        | Circulating level ↑ | CrGN and DKD | | [67, 68] |
| VEGF-C        | Circulating level ↑ | CKD | A potential new biomarker of hypervolemia | [70] |
| VEGF-B, VEGF-D| Circulating level ↑ | DKD | Correlated with renal dysfunction | [71, 72] |
| PGF           | Circulating level ↑ | Adult men (ULSAM) Biopsy-confirmed kidney disease Cardiac surgery | Predictor of CKD incidence Top biomarker for kidney disease progression Associated with lower odds of AKI, long AKI duration, and mortality | [74–76] |
| IGF-1         | Circulating level ↓ | AKI | Candidate as an early and sensitive biomarker for AKI mortality in ICU | [3] |
| IGFBP-7       | Urinary level ↑ | AKI Cardiac surgery Sepsis | Combine with TIMP-2 as biomarker for risk assessment of AKI in ICU (approved) | [81] |
| CTGF          | Circulating level ↑ | CKD | An independent predictor for ESRD | [82] |
| PDGF-D        | Circulating level ↑ | IgA nephropathy | | [7] |
| PDGF-A        | Urinary level ↑ | Uncomplicated T1D | Associated with hyperfiltration | [7] |
| PGRN          | Circulating level ↑ | AKI, CKD | | [90] |
| MYDGF         | Circulating level ↓ | DKD | | [96] |

BMP7, bone morphogenetic protein 7; GDF15, growth differentiation factor 15; EGF, epidermal growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; PGF, placental growth factor; IGF-1, insulin-like growth factor-1; IGFBP-7, insulin-like growth factor-binding protein-7; CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor; PGRN, progranulin; MYDGF, myeloid-derived growth factor; T2D, type 2 diabetes; CKD, chronic kidney disease; DKD, diabetic kidney disease; GFR, glomerular filtration rate; AKI, acute kidney injury; UPJO, ureteropelvic junction obstruction; RRT, renal replacement therapies; CrGN, crescentic glomerulonephritis; ULSAM, Uppsala Longitudinal Study of Adult Men; T1D, type 1 diabetes; ICU, intensive care unit; TIMP-2, tissue inhibitor of metalloproteinase-2; ESRD, end-stage renal disease.
pressed in renal parenchymal cells and is significantly reduced in podocytes from mice with FSGS and DKD [98]. The levels of MYDGF in glomeruli are negatively correlated with urinary albumin:creatinine ratio in mice with glomerular diseases [98]. Functionally, MYDGF protects podocytes against mitotic catastrophe by reducing accumulation of podocytes in S phase [98]. More importantly, a significant reduction of MYDGF is found in glomeruli from patients with glomerular disease, and the level of MYDGF is correlated with GFR, serum creatinine, and podocyte loss, indicating that MYDGF may be an attractive therapeutic target for glomerular disease [98].

Conclusions
For decades, the value of growth factors as biomarkers and therapeutic targets for kidney diseases has attracted much attention. Many growth factors have shown their potential as biomarkers for the clinical diagnosis of kidney diseases (Table 1). Nevertheless, subsequent investigations with large cohorts and long follow-up are required to more accurately define the application value of a certain growth factor in specific stage of certain kidney diseases. On the other hand, further assessment of broader combinations of biomarkers containing appropriate growth factors will contribute to the precise diagnosis of kidney diseases. In the aspect of therapeutic targets for kidney diseases (Table 2), approach targeting growth factors has not yet translated into an effective and safe therapeutic strategy in humans, which may be due to the heterogeneity of kidney diseases and the pluripotency of growth factors. In the future, the therapies of kidney diseases tend to be individualized, which may provide a novel strategy for the treatment of kidney diseases.
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Author Contributions

Wei Tang wrote the manuscript; Yufeng Zhang and Sijia Cui prepared the figures and tables; and Fan Yi decided on the topics and wrote the manuscript.

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