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.

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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-

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Fig. 1. Simplified overview of the growth factors and their actions in kidney diseases discussed in the present review. BMP7, EGF, HGF, VEGF, PGRN, and MYDGF are renoprotective proteins. Their levels are decreased (green) in different kidney diseases which are associated with the damage of renal parenchymal cells due to enhanced cell death and inflammatory responses, and insufficient repair. Under physiological conditions, VEGF-A secreted by podocytes binds to VEGFRs on GEnC and stimulates GEnC proliferation, migration, and survival. TGF-β, CTGF, PDGF, activin A, and activin B are all pro-fibrotic growth factors. Their elevated expression (red) in kidney diseases will lead to renal fibrosis by promoting the activation of interstitial fibroblasts and/or mesangial cells. Activin A affects renal cells, such as renal interstitial fibroblasts, tubular and mesangial cells and promotes fibrosis directly or through mediating TGF-β1 responses. Activin B is produced mainly in TECs, but its effector cells are interstitial fibroblasts.
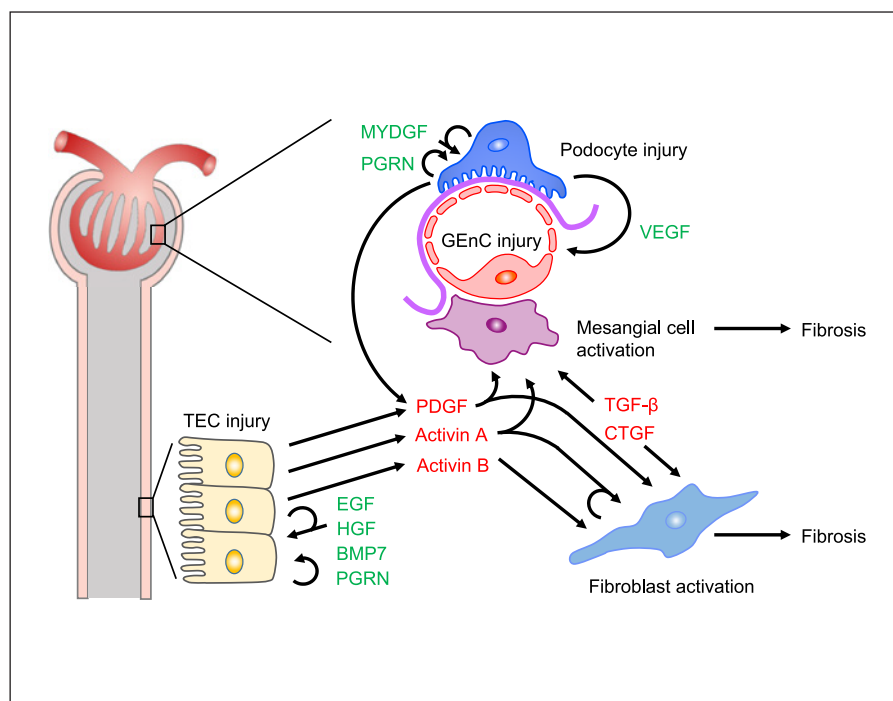
while, currently there is no satisfactory clinical treatment available to prevent or treat kidney disease because of the poor therapeutic efficacy and systemic side effects. Therefore, strategies to establish early diagnosis, identify the key molecules, and develop novel therapeutic interventions to 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 ap-

plication 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 fresolimumab 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-
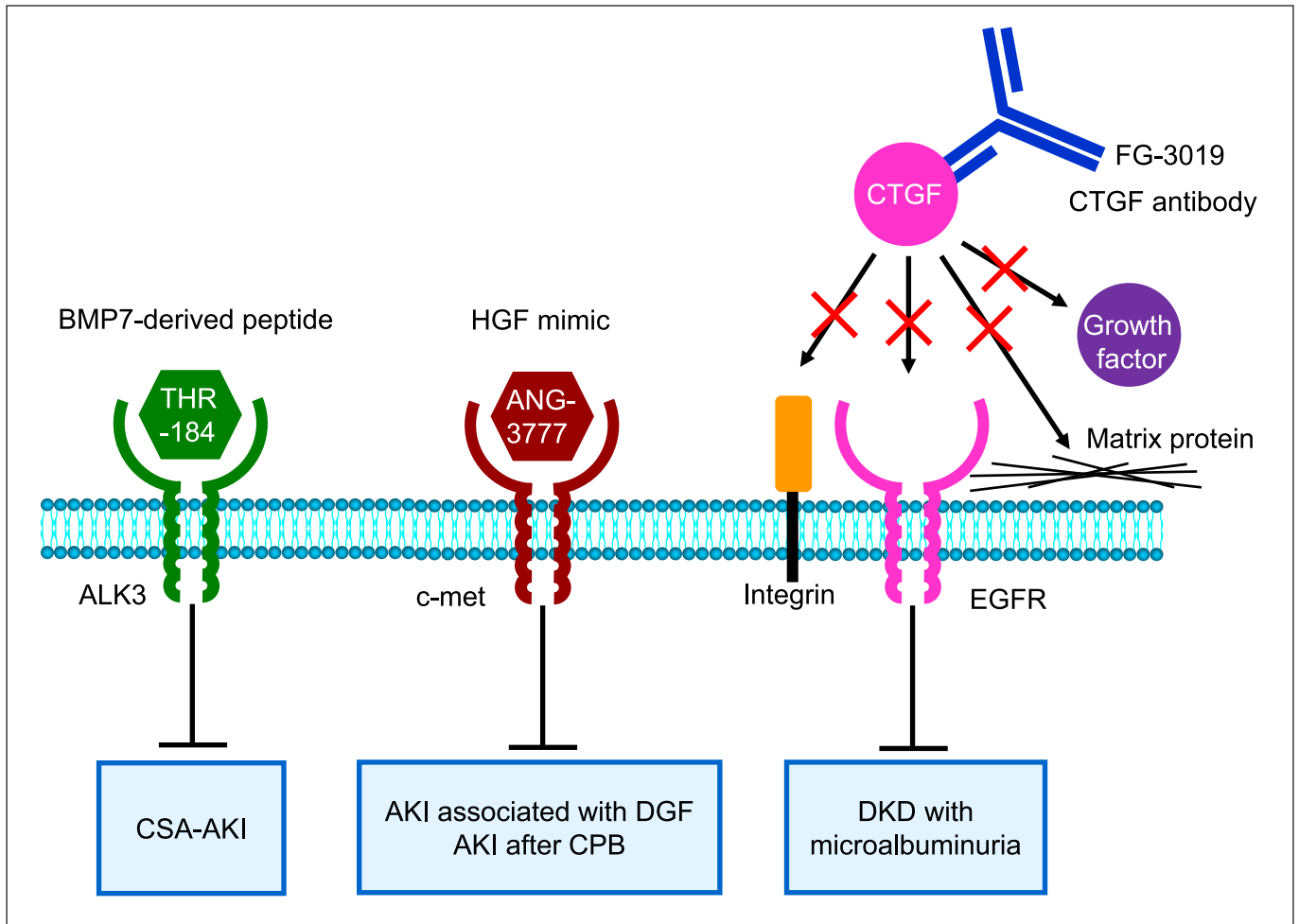
Fig. 2. Therapeutic agents targeting BMP7, HGF, and CTGF for kidney diseases in clinical trials. The BMP7-derived small peptide THR-184 is an agonist of BMP7 receptor ALK3 and has been tested for the prevention of cardiac surgery-associated acute kidney injury (CSA-AKI). ANG-3777, a HGF mimetic, can 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.

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

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 nephroprotective [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 α 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

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 FGFRL1 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]. The high cir-

culating FGF23 levels are harmful to erythropoiesis, the cardiovascular system, and the immune system, which can lead to adverse progression of CKD. The renal FGF23 expression also increases in kidney diseases, which may promote the inflammatory response and fibrosis process in the kidney [54]. Different therapeutic strategies targeting FGF23 have been developed such as FGF23 antibody. However, blocking FGF23 by antibody exacerbates hyperphosphatemia and vascular calcification which may cause an increased risk of mortality in CKD patients [47]. Furthermore, several clinical trials have been conducted to evaluate the effects of strategies targeting dietary phosphate, such as phosphate binder, on the reduction of FGF23 in CKD [51]. In AKI, FGF23 is significantly increased in the circulation and urine of patients and animal models induced by multiple insults [3, 47]. Therefore, FGF23 can serve as an early prognostic marker for incident AKI, and a candidate prognostic marker for adverse outcomes in patients with established AKI [47]. Whether FGF23 plays a functional role in mediating AKI remains to be explored.

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 and TECs [3, 12]. In patients that had AKI and required renal replacement therapies in the intensive care units (ICUs), the decreased levels of urinary neutrophil gelatinase-associated lipocalin (NGAL) and urinary HGF in the first 14 days are associated with an increased probability of renal recovery [56]. Preclinical studies have demonstrated the renoprotective role of HGF in a variety of animal models of AKI and CKD, exerting anti-inflammatory and regenerative effects and preventing tubular cell apoptosis, epithelial-to-mesenchymal transition, and fibrosis [12]. In addition, conditional knockout of renal tubule c-met substantially aggravates renal injury in AKI mouse model, indicating a protective role of tubule-specific c-met signaling [3]. Therefore, HGF and c-met become ideal targets for the treatment of kidney diseases.

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 in 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 stimulates 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-A$_{165}$ 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-A$_{xxx}$b [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

VEGF-A$_{165}$b isoform relative to VEGF-A$_{165}$. However, during the later stages of DKD, when estimated GFR has declined, the increased expression of VEGF-A$_{165}$b is diminished [69]. Podocyte-specific overexpression of VEGF-A$_{165}$b 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 FGF23 are significantly associated with estimated GFR decline per year in the replication cohort from the Uppsala Longitudinal Study of Adult Men (UL-SAM), 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-

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/PDGF-B 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 aggra-

vates 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/FoxO1 signaling-mediated mitochondrial biogenesis and mitophagy and induces autophagy via CaMKK-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 marrow chimeric mice, the role 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 ↑ / Urinary 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 ↑ / Urinary 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	Predictor of CKD incidence / Top biomarker for kidney disease progression	[74–76]
		Cardiac surgery	Associated with lower odds of AKI, long AKI duration, and mortality	
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 ↑ / Urinary 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.

Table 2. Summary of relevant clinical trials for the treatment of kidney diseases targeting growth factors

Agent/mechanism of action	Type	Kidney disease	Outcome	Clinical trial identifier (http://www.clinicaltrials.gov)
Fresolimumab/TGF-β antagonists	Antibody	FSGS Primary FSGS	Phase 1: slowed the rate down of GFR decrease Phase 2: no effect on proteinuria reduction	NCT00464321 NCT01665391
LY2382770/TGF-β antagonists	Antibody	DKD	Phase 2: terminated due to lack of efficacy	NCT01113801
THR-184/BMP receptor agonist (ALK3 agonist)	Small peptide	CSA-AKI	Phase 2: no effects on the incidence, severity, or duration of AKI	NCT01830920
ANG-3777/HGF-like molecule, c-met agonist	Small molecule	Renal transplant recipients with signs of DGF DGF AKI	Phase 2: increased urine output, lower serum creatinine, and reduced need for dialysis Phase 3: active, not recruiting Phase 2: active, not recruiting	NCT01286727 NCT02474667 NCT02771509
FG-3019/CTGF inhibitor	Antibody	Diabetes mellitus and DKD FSGS DKD	Phase 1: reduced microalbuminuria Phase 1: prematurely stopped for unknown reasons Phase 2: prematurely stopped for suboptimal study design	NCT00102297 NCT00754143 NCT00782561 NCT00913393

TGF-β, transforming growth factor beta; BMP, bone morphogenetic protein; ALK3, activin-like kinase-3 receptor; HGF, hepatocyte growth factor; CTGF, connective tissue growth factor; FSGS, focal segmental glomerulosclerosis; DKD, diabetic kidney disease; CSA-AKI, cardiac surgery-associated acute kidney injury; DGF, delayed graft function; AKI, acute kidney injury; GFR, glomerular filtration rate.

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 podocyte 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 of 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 disease. 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 requires the deployment of different combinations of agents for different clinical scenarios. Therefore, many attempts should be made to optimize the therapeutic agents to achieve highly specific, durable, and beneficial effects and avoid their side effects. In parallel, cell-based therapy and nucleic acid therapeutics are attractive approaches to facilitate the clinical translation of growth factor-targeted therapy of kidney diseases, which may provide a novel strategy for the treatment of kidney diseases.

Conflict of Interest Statement

Dr. Fan Yi is an Associate Editor 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.

References

1 Guzeloglu-Kayisli O, Kayisli UA, Taylor HS. The role of growth factors and cytokines during implantation: endocrine and paracrine interactions. Semin Reprod Med. 2009 Jan; 27(1):62–79.

2 Silva AC, Lobo JMS. Cytokines and growth factors. Adv Biochem Eng Biotechnol. 2020; 171:87–113.

3 Gao L, Zhong X, Jin J, Li J, Meng XM. Potential targeted therapy and diagnosis based on novel insight into growth factors, receptors, and downstream effectors in acute kidney injury and acute kidney injury-chronic kidney disease progression. Signal Transduct Target Ther. 2020 Feb 14;5(1):9.

4 Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020 May;16(5):269–88.

5 Allinovi M, De Chiara L, Angelotti ML, Becherucci F, Romagnani P. Anti-fibrotic treatments: a review of clinical evidence. Matrix Biol. 2018 Aug–69:333–54.

6 Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. Nat Rev Nephrol. 2016 Jun;12(6):325–38.

7 Kok HM, Falke LL, Goldschmeding R, Nguyen TQ. Targeting CTGF, EGF and PDGF pathways to prevent progression of kidney disease. Nat Rev Nephrol. 2014 Dec;10(12): 700–11.

8 Nguyen TQ, Goldschmeding R. Bone morphogenetic protein-7 and connective tissue growth factor: novel targets for treatment of renal fibrosis? Pharm Res. 2008 Oct;25(10): 2416–26.

9 Nakamura J, Yanagita M. Bmp modulators in kidney disease. Discov Med. 2012 Jan;13(68): 57–63.

10 Li RX, Yiu WH, Tang SCW. Role of bone morphogenetic protein-7 in renal fibrosis. Front Physiol. 2015;6:114.

11 Wong MG, Perkovic V, Woodward M, Chalmers J, Li Q, Hillis GS, et al. Circulating bone morphogenetic protein-7 and transforming growth factor-β1 are better predictors of renal end points in patients with type 2 diabetes mellitus. Kidney Int. 2013 Feb; 83(2):278–84.

12 Benoit SW, Devarajan P. Acute kidney injury: emerging pharmacotherapies in current clinical trials. Pediatr Nephrol. 2018 May;33(5): 779–87.

13 McVicker BL, Bennett RG. Novel anti-fibrotic therapies. Front Pharmacol. 2017;8:318.

14 Nastase MV, Zeng-Brouwers J, Wygrecka M, Schaefer L. Targeting renal fibrosis: mechanisms and drug delivery systems. Adv Drug Deliv Rev. 2018 Apr;129:295–307.

15 Gallagher KM, O'Neill S, Harrison EM, Ross JA, Wigmore SJ, Hughes J. Recent early clinical drug development for acute kidney injury. Expert Opin Investig Drugs. 2017 Feb;26(2): 141–54.

16 Himmelfarb J, Chertow GM, McCullough PA, Mesana T, Shaw AD, Sundt TM, et al. Perioperative THR-184 and AKI after cardiac surgery. J Am Soc Nephrol. 2018 Feb;29(2): 670–9.

17 Emmerson PJ, Duffin KL, Chintharlapalli S, Wu X. GDF15 and growth control. Front Physiol. 2018;9:1712.

18 Perez-Gomez MV, Pizarro-Sanchez S, Gracia-Iguacel C, Cano S, Cannata-Ortiz P, Sanchez-Rodriguez J, et al. Urinary growth differentiation factor-15 (GDF15) levels as a biomarker of adverse outcomes and biopsy findings in chronic kidney disease. J Nephrol. 2021 Dec;34(6):1819–32.

19 Mazagova M, Buikema H, van Buiten A, Duin M, Goris M, Sandovici M, et al. Genetic deletion of growth differentiation factor 15 augments renal damage in both type 1 and type 2 models of diabetes. Am J Physiol Renal Physiol. 2013 Nov 1;305(9):F1249–64.

20 Kim YI, Shin HW, Chun YS, Park JW. CST3 and GDF15 ameliorate renal fibrosis by inhibiting fibroblast growth and activation. Biochem Biophys Res Commun. 2018 Jun 2; 500(2):288–95.

21 Liu J, Kumar S, Heinzel A, Gao M, Guo J, Alvarado GF, et al. Renoprotective and immunomodulatory effects of GDF15 following AKI Invoked by ischemia-reperfusion injury. J Am Soc Nephrol. 2020 Apr;31(4):701–15.

22 Valino-Rivas L, Cuarental L, Ceballos MI, Pintor-Chocano A, Perez-Gomez MV, Sanz AB, et al. Growth differentiation factor-15 preserves Klotho expression in acute kidney injury and kidney fibrosis. Kidney Int. 2022 Mar 23;101(6):1200–15.

23 Hellemons ME, Mazagova M, Gansevoort RT, Henning RH, de Zeeuw D, Bakker SJL, et al. Growth-differentiation factor 15 predicts worsening of albuminuria in patients with type 2 diabetes. Diabetes Care. 2012 Nov; 35(11):2340–6.

24 Bidadkosh A, Lambooy SPH, Heerspink HJ, Pena MJ, Henning RH, Buikema H, et al. Predictive properties of biomarkers GDF-15, NTproBNP, and hs-TnT for morbidity and mortality in patients with type 2 diabetes with nephropathy. Diabetes Care. 2017 Jun;40(6): 784–92.

25 Lajer M, Jorsal A, Tarnow L, Parving HH, Rossing P. Plasma growth differentiation factor-15 independently predicts all-cause and cardiovascular mortality as well as deterioration of kidney function in type 1 diabetic patients with nephropathy. Diabetes Care. 2010 Jul;33(7):1567–72.

26 Simonson MS, Tiktin M, Debanne SM, Rahman M, Berger B, Hricik D, et al. The renal transcriptome of db/db mice identifies putative urinary biomarker proteins in patients with type 2 diabetes: a pilot study. Am J Physiol Renal Physiol. 2012 Apr 1;302(7):F820–9.

27 Namwanje M, Brown CW. Activins and inhibins: roles in development, physiology, and disease. Cold Spring Harb Perspect Biol. 2016 Jul 1;8(7):a021881.

28 Mehta N, Krepinsky JC. The emerging role of activins in renal disease. Curr Opin Nephrol Hypertens. 2020 Jan;29(1):136–44.

29 Yamashita S, Maeshima A, Kojima I, Nojima Y. Activin a is a potent activator of renal interstitial fibroblasts. J Am Soc Nephrol. 2004 Jan;15(1):91–101.

30 Zhang D, Gava AL, Van Krieken R, Mehta N, Li R, Gao B, et al. The caveolin-1 regulated protein follistatin protects against diabetic kidney disease. Kidney Int. 2019 Nov;96(5): 1134–49.

31 Maeshima A, Mishima K, Yamashita S, Nakasatomi M, Miya M, Sakurai N, et al. Follistatin, an activin antagonist, ameliorates renal interstitial fibrosis in a rat model of unilateral ureteral obstruction. Biomed Res Int. 2014;2014:376191.

32 Gaedeke J, Boehler T, Budde K, Neumayer HH, Peters H. Glomerular activin A overexpression is linked to fibrosis in anti-Thy1 glomerulonephritis. Nephrol Dial Transplant. 2005 Feb;20(2):319–28.

33 Williams MJ, Sugatani T, Agapova OA, Fang Y, Gaut JP, Faugere MC, et al. The activin receptor is stimulated in the skeleton, vasculature, heart, and kidney during chronic kidney disease. Kidney Int. 2018 Jan;93(1):147–58.

34 Agapova OA, Fang Y, Sugatani T, Seifert ME, Hruska KA. Ligand trap for the activin type IIA receptor protects against vascular disease and renal fibrosis in mice with chronic kidney disease. Kidney Int. 2016 Jun;89(6): 1231–43.

35 Wada W, Kuwano H, Hasegawa Y, Kojima I. The dependence of transforming growth factor-beta-induced collagen production on autocrine factor activin A in hepatic stellate cells. Endocrinology. 2004 Jun;145(6):2753–9.

36 Ren XJ, Guan GJ, Liu G, Zhang T, Liu GH. Effect of activin A on tubulointerstitial fibrosis in diabetic nephropathy. Nephrology. 2009 Apr;14(3):311–20.

37 Sun Y, Cai H, Ge J, Shao F, Huang Z, Ding Z, et al. Tubule-derived INHBB promotes interstitial fibroblast activation and renal fibrosis. J Pathol. 2022 Jan;256(1):25–37.

38 Chen J, Chen JK, Harris RC. Deletion of the epidermal growth factor receptor in renal proximal tubule epithelial cells delays recovery from acute kidney injury. Kidney Int. 2012 Jul;82(1):45–52.

39 Ju W, Nair V, Smith S, Zhu L, Shedden K, Song PXK, et al. Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker. Sci Transl Med. 2015 Dec 2;7(316):316ra193.

40 Klein J, Bascands JL, Buffin-Meyer B, Schanstra JP. Epidermal growth factor and kidney disease: a long-lasting story. Kidney Int. 2016 May;89(5):985–7.

41 Worawichawong S, Worawichawong S, Radinahamed P, Muntham D, Sathirapongsasuti N, Nongnuch A, et al. Urine epidermal growth factor, monocyte chemoattractant protein-1 or their ratio as biomarkers for interstitial fibrosis and tubular atrophy in primary glomerulonephritis. Kidney Blood Press Res. 2016;41(6):997–1007.

42 Satirapoj B, Dispan R, Radinahamed P, Kitiyakara C. Urinary epidermal growth factor, monocyte chemoattractant protein-1 or their ratio as predictors for rapid loss of renal function in type 2 diabetic patients with diabetic kidney disease. BMC Nephrol. 2018 Sep 21; 19(1):246.

43 Wu L, Li XQ, Chang DY, Zhang H, Li JJ, Wu SL, et al. Associations of urinary epidermal growth factor and monocyte chemotactic protein-1 with kidney involvement in patients with diabetic kidney disease. Nephrol Dial Transplant. 2020 Feb 1;35(2):291–7.

44 Torres DD, Rossini M, Manno C, Mattace-Raso F, D'Altri C, Ranieri E, et al. The ratio of epidermal growth factor to monocyte chemotactic peptide-1 in the urine predicts renal prognosis in IgA nephropathy. Kidney Int. 2008 Feb;73(3):327–33.

45 Menez S, Ju W, Menon R, Moledina DG, Thiessen Philbrook H, McArthur E, et al. Urinary EGF and MCP-1 and risk of CKD after cardiac surgery. JCI Insight. 2021 Jun 8;6(11): e147464.

46 Norvik JV, Harskamp LR, Nair V, Shedden K, Solbu MD, Eriksen BO, et al. Urinary excretion of epidermal growth factor and rapid loss of kidney function. Nephrol Dial Transplant. 2021 Sep 27;36(10):1882–92.

47 Xie Y, Su N, Yang J, Tan Q, Huang S, Jin M, et al. FGF/FGFR signaling in health and disease. Signal Transduct Target Ther. 2020 Sep 2;5(1):181.

48 Anuwatmatee S, Tang S, Wu BJ, Rye KA, Ong KL. Fibroblast growth factor 21 in chronic kidney disease. Clin Chim Acta. 2019 Feb; 489:196–202.

49 Trakarnvanich T, Prommool S, Kurathong S, Teepprasan T, Wang Y. Associations among cardio-ankle vascular index, carotid intima-media thickness, and fibroblast growth factor-21 levels in kidney transplant patients. Transplant Proc. 2017 Oct;49(8):1791–6.

50 Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, et al. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metab. 2013 Sep 3; 18(3):333–40.

51 Musgrove J, Wolf M. Regulation and effects of FGF23 in chronic kidney disease. Annu Rev Physiol. 2020 Feb 10;82(1):365–90.

52 Desjardins L, Liabeuf S, Renard C, Lenglet A, Lemke HD, Choukroun G, et al. FGF23 is independently associated with vascular calcification but not bone mineral density in patients at various CKD stages. Osteoporos Int. 2012 Jul;23(7):2017–25.

53 Shimamura Y, Hamada K, Inoue K, Ogata K, Ishihara M, Kagawa T, et al. Serum levels of soluble secreted alpha-Klotho are decreased in the early stages of chronic kidney disease, making it a probable novel biomarker for early diagnosis. Clin Exp Nephrol. 2012 Oct; 16(5):722–9.

54 Mace ML, Olgaard K, Lewin E. New aspects of the kidney in the regulation of fibroblast growth factor 23 (FGF23) and mineral homeostasis. Int J Mol Sci. 2020 Nov 20;21(22):8810.

55 Organ SL, Tsao MS. An overview of the c-MET signaling pathway. Ther Adv Med Oncol. 2011 Nov;3(Suppl 1):S7–19.

56 Srisawat N, Wen X, Lee M, Kong L, Elder M, Carter M, et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol. 2011 Aug; 6(8):1815–23.

57 Hulse M, Rosner MH. Drugs in development for acute kidney injury. Drugs. 2019 Jun; 79(8):811–21.

58 Bromberg JS, Weir MR, Gaber AO, Yamin MA, Goldberg ID, Mayne TJ, et al. Renal function improvement following ANG-3777 treatment in patients at high risk for delayed graft function after kidney transplantation. Transplantation. 2021 Feb 1;105(2):443–50.

59 Vincenti F, Kim J, Gouveia D, Pelle G, Mayne TJ, Neylan JF. Phase 3 trial design of the hepatocyte growth factor mimetic ANG-3777 in renal transplant recipients with delayed graft function. Kidney Int Rep. 2021 Feb;6(2):296–303.

60 Ayad S, Neylan JF, Mayne TJ, Gouveia D, Swaminathan M. Hepatocyte growth factor mimetic ANG-3777 for cardiac surgery-associated acute kidney injury. Kidney Int Rep. 2020 Dec;5(12):2325–32.

61 Kikuchi R, Stevens M, Harada K, Oltean S, Murohara T. Anti-angiogenic isoform of vascular endothelial growth factor-A in cardiovascular and renal disease. Adv Clin Chem. 2019;88:1–33.

62 Stevens M, Oltean S. Alternative splicing in CKD. J Am Soc Nephrol. 2016 Jun;27(6): 1596–603.

63 Bartlett CS, Jeansson M, Quaggin SE. Vascular growth factors and glomerular disease. Annu Rev Physiol. 2016;78:437–61.

64 Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med. 2008 Mar 13;358(11): 1129–36.

65 Martini S, Nair V, Keller BJ, Eichinger F, Hawkins JJ, Randolph A, et al. Integrative biology identifies shared transcriptional networks in CKD. J Am Soc Nephrol. 2014 Nov; 25(11):2559–72.

66 Kikuchi R, Yasuda Y, Nakatochi M, Shibata Y, Hara T, Suzuki A, et al. Urinary and circulating levels of the anti-angiogenic isoform of vascular endothelial growth factor-A in patients with chronic kidney disease. Clin Chim Acta. 2017 Dec;475:102–8.

67 Nitta K, Uchida K, Kimata N, Honda K, Horita S, Hayashi T, et al. Increased serum levels of vascular endothelial growth factor in human crescentic glomerulonephritis. Clin Nephrol. 1999 Aug;52(2):76–82.

68 Hovind P, Tarnow L, Oestergaard PB, Parving HH. Elevated vascular endothelial growth factor in type 1 diabetic patients with diabetic nephropathy. Kidney Int Suppl. 2000 Apr;75:S56–61.

69 Oltean S, Qiu Y, Ferguson JK, Stevens M, Neal C, Russell A, et al. Vascular endothelial growth factor-A165b is protective and restores endothelial glycocalyx in diabetic nephropathy. J Am Soc Nephrol. 2015 Aug; 26(8):1889–904.

70 Sahutoglu T, Sakaci T, Hasbal NB, Ahbap E, Kara E, Sumerkan MC, et al. Serum VEGF-C levels as a candidate biomarker of hypervolemia in chronic kidney disease. Medicine. 2017 May;96(18):e6543.

71 Wei Y, Han S, Zhou R, Xu P, Zhou L, Zhu Z, et al. Increased serum VEGF-B level is associated with renal function impairment in patients with type 2 diabetes. Front Endocrinol. 2022;13:862545.

72 Nguyen TTU, Kim H, Chae YJ, Jung JH, Kim W. Serum VEGF-D level is correlated with renal dysfunction and proteinuria in patients with diabetic chronic kidney disease. Medicine. 2022 Feb 18;101(7):e28804.

73 Lee AS, Lee JE, Jung YJ, Kim DH, Kang KP, Lee S, et al. Vascular endothelial growth factor-C and -D are involved in lymphangiogenesis in mouse unilateral ureteral obstruction. Kidney Int. 2013 Jan;83(1):50–62.

74 Carlsson AC, Ingelsson E, Sundstrom J, Carrero JJ, Gustafsson S, Feldreich T, et al. Use of proteomics to investigate kidney function decline over 5 years. Clin J Am Soc Nephrol. 2017 Aug 7;12(8):1226–35.

75 Schmidt IM, Sarvode Mothi S, Wilson PC, Palsson R, Srivastava A, Onul IF, et al. Circulating plasma biomarkers in biopsy-confirmed kidney disease. Clin J Am Soc Nephrol. 2022 Jan;17(1):27–37.

76 Mansour SG, Zhang WR, Moledina DG, Coca SG, Jia Y, Thiessen-Philbrook H, et al. The association of angiogenesis markers with acute kidney injury and mortality after cardiac surgery. Am J Kidney Dis. 2019 Jul;74(1):36–46.

77 Bach LA. The insulin-like growth factor system in kidney disease and hypertension. Curr Opin Nephrol Hypertens. 2012 Jan;21(1):86–91.

78 Bach LA, Hale LJ. Insulin-like growth factors and kidney disease. Am J Kidney Dis. 2015 Feb;65(2):327–36.

79 Flyvbjerg A. Putative pathophysiological role of growth factors and cytokines in experimental diabetic kidney disease. Diabetologia. 2000 Oct;43(10):1205–23.

80 Maximus PS. Insulin like growth factor 1 is linked to higher cardiovascular risk score in adults with type 2 diabetes mellitus and chronic kidney disease. Diabetes Metab Syndr. 2019 Jul–Aug;13(4):2613–8.

81 Wang S, Chi K, Wu D, Hong Q. Insulin-like growth factor binding proteins in kidney disease. Front Pharmacol. 2021;12:807119.

82 Nguyen TQ, Tarnow L, Jorsal A, Oliver N, Roestenberg P, Ito Y, et al. Plasma connective tissue growth factor is an independent predictor of end-stage renal disease and mortality in type 1 diabetic nephropathy. Diabetes Care. 2008 Jun;31(6):1177–82.

83 Floege J, Eitner F, Alpers CE. A new look at platelet-derived growth factor in renal disease. J Am Soc Nephrol. 2008 Jan;19(1):12–23.

84 Ostendorf T, Kunter U, Grone HJ, Bahlmann F, Kawachi H, Shimizu F, et al. Specific antagonism of PDGF prevents renal scarring in experimental glomerulonephritis. J Am Soc Nephrol. 2001 May;12(5):909–18.

85 Suzuki H, Usui I, Kato I, Oya T, Kanatani Y, Yamazaki Y, et al. Deletion of platelet-derived growth factor receptor-β improves diabetic nephropathy in Ca2+/calmodulin-dependent protein kinase IIα (Thr286Asp) transgenic mice. Diabetologia. 2011 Nov;54(11):2953–62.

86 Zhou M, Tang W, Fu Y, Xu X, Wang Z, Lu Y, et al. Progranulin protects against renal ischemia/reperfusion injury in mice. Kidney Int. 2015 May;87(5):918–29.

87 Wang X, Yi F. The nucleotide oligomerization domain-like receptors in kidney injury. Kidney Dis. 2016 Apr;2(1):28–36.

88 Zhou D, Zhou M, Wang Z, Fu Y, Jia M, Wang X, et al. PGRN acts as a novel regulator of mitochondrial homeostasis by facilitating mitophagy and mitochondrial biogenesis to prevent podocyte injury in diabetic nephropathy. Cell Death Dis. 2019 Jul 8;10(7):524.

89 Zhou D, Zhou M, Wang Z, Fu Y, Jia M, Wang X, et al. Progranulin alleviates podocyte injury via regulating CAMKK/AMPK-mediated autophagy under diabetic conditions. J Mol Med. 2019 Nov;97(11):1507–20.

90 Ebert T, Kralisch S, Kloting N, Hoffmann A, Bluher M, Zhang MZ, et al. Circulating progranulin but not renal progranulin expression is increased in renal dysfunction. Kidney Int. 2015 Nov;88(5):1197–8.

91 Korf-Klingebiel M, Reboll MR, Klede S, Brod T, Pich A, Polten F, et al. Myeloid-derived growth factor (C19orf10) mediates cardiac repair following myocardial infarction. Nat Med. 2015 Feb;21(2):140–9.

92 Yuan Z, Tsou YH, Zhang XQ, Huang S, Yang Y, Gao M, et al. Injectable citrate-based hydrogel as an angiogenic biomaterial improves cardiac repair after myocardial infarction. ACS Appl Mater Interfaces. 2019 Oct 23; 11(42):38429–39.

93 Wang Y, Li Y, Feng J, Liu W, Li Y, Liu J, et al. Mydgf promotes cardiomyocyte proliferation and neonatal heart regeneration. Theranostics. 2020;10(20):9100–12.

94 Meng B, Li Y, Ding Y, Xu X, Wang L, Guo B, et al. Myeloid-derived growth factor inhibits inflammation and alleviates endothelial injury and atherosclerosis in mice. Sci Adv. 2021 May;7(21):eabe6903.

95 Korf-Klingebiel M, Reboll MR, Polten F, Weber N, Jackle F, Wu X, et al. Myeloid-derived growth factor protects against pressure overload-induced heart failure by preserving sarco/endoplasmic reticulum Ca(2+)-ATPase expression in cardiomyocytes. Circulation. 2021 Oct 12;144(15):1227–40.

96 He M, Li Y, Wang L, Guo B, Mei W, Zhu B, et al. MYDGF attenuates podocyte injury and proteinuria by activating Akt/BAD signal pathway in mice with diabetic kidney disease. Diabetologia. 2020 Sep;63(9):1916–31.

97 Wang L, Li Y, Guo B, Zhang J, Zhu B, Li H, et al. Myeloid-derived growth factor promotes intestinal glucagon-like peptide-1 production in male mice with type 2 diabetes. Endocrinology. 2020 Feb 1;161(2):bqaa003.

98 Zhan P, Zhang Y, Shi W, Liu X, Qiao Z, Wang Z, et al. Myeloid-derived growth factor deficiency exacerbates mitotic catastrophe of podocytes in glomerular disease. Kidney Int. 2022 May 25:S0085-2538(22)00377-5.