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Review article

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Advances and challenges in kidney fibrosis therapeutics

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Abstract

Chronic kidney disease (CKD) is a major global health burden that affects more than 10% of the adult population. Current treatments, including dialysis and transplantation, are costly and not curative. Kidney fibrosis, defined as an abnormal accumulation of extracellular matrix in the kidney parenchyma, is a common outcome in CKD, regardless of disease aetiology, and is a major cause of loss of kidney function and kidney failure. For this reason, research efforts have focused on identifying mediators of kidney fibrosis to inform the development of effective anti-fibrotic treatments. Given the prominent role of the transforming growth factor-β (TGFβ) family in fibrosis, efforts have focused on inhibiting TGFβ signalling. Despite hopes raised by the efficacy of this approach in preclinical models, translation into clinical practice has not met expectations. Antihypertensive and antidiabetic drugs slow the decline in kidney function and could slow fibrosis but, owing to the lack of technologies for in vivo renal imaging, their anti-fibrotic effect cannot be truly assessed at present. The emergence of new drugs targeting pro-fibrotic signalling, or enabling cell repair and cell metabolic reprogramming, combined with better stratification of people with CKD and the arrival of nanotechnologies for kidney-specific drug delivery, open up new perspectives for the treatment of this major public health challenge.

Sections

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Key points

- Regardless of aetiology, progressive chronic kidney disease typically leads to the development of kidney fibrosis, which remains a challenge for public health.
- Transforming growth factor-β is a key mediator of kidney fibrosis but therapies targeting this pathway have failed to show benefit or had only a limited effect in people with chronic kidney disease.
- Anti-fibrotic treatments that have been successful in other organs, such as the lungs or liver, provide promising alternatives for testing in kidney fibrosis.
- Therapies for hypertension or diabetes have benefits beyond their primary targets and show clear nephroprotection, which ultimately affects kidney fibrosis.
- Development of novel technologies such as non-invasive imaging, or the use of Janus or exosome-like nanoparticles, provide new opportunities for assessing and treating kidney fibrosis.

Introduction

Chronic kidney disease (CKD) is a leading cause of disability worldwide owing to an ageing population, improved survival from cardiovascular disease, the increased prevalence of type 2 diabetes and a rise in autoimmune disorders driven by environmental changes (including pollution and industrialized food systems)[1]. Current estimates indicate that more than 10% of the adult population has CKD[2]. Although the initiating cause might differ, the progression of CKD converges towards common pathological mechanisms such as chronic inflammation and an excessive accumulation of extracellular matrix (ECM), which disrupt the normal structure of the kidney. Over time, this deleterious effect leads to kidney failure (also known as end-stage kidney disease). Despite extensive investigation and remarkable progress in understanding the mechanisms leading to kidney failure, the only treatments currently available for kidney failure are dialysis or transplantation, which are kidney replacement strategies and not restorative therapies. In addition to reducing the quality of life of patients, these strategies absorb up to 4% of the total health budget in high-resource countries, making kidney failure the most costly disease per patient[2]. Therefore, finding effective treatments to stop or even reverse the progression of kidney disease constitutes a major public health challenge.

Over the past decade, interest in identifying new mediators of kidney fibrosis to inform the development of anti-fibrotic treatments has continued to grow (Fig. 1). Antihypertensive drugs, mainly those blocking the renin–angiotensin–aldosterone system (RAAS) were very efficient in reversing kidney fibrosis and restoring kidney function in several animal models, but these anti-fibrotic benefits were not confirmed in clinical trials[3,4]. However, the development of glucose transporter inhibitors with beneficial effects beyond diabetes, the synthesis of anti-inflammatory agents with increased specificity against pro-inflammatory mediators, the improvement of inhibitors of other vasoconstrictors and the development of cutting-edge technologies for the specific targeting of tissues, cells, proteins and/or genes, have provided new therapeutic options and renewed hope for the development of a treatment for kidney fibrosis.

In this Review, we briefly discuss key mediators and mechanisms involved in the creation and development of a fibrous microenvironment in the kidney. We then examine studies of anti-fibrotic drugs that were unsuccessfully applied to the kidney, and others that have succeeded in other tissues and have potential against kidney fibrosis. We also consider advances in nephroprotective strategies that combine newly developed anti-diabetic and/or anti-inflammatory treatments with RAAS blockers, which might halt kidney fibrosis or even lead to its regression. Finally, we discuss technologies with therapeutic potential in targeting different pro-fibrotic factors and pathways in the kidney.

Kidney fibrosis niche and therapeutic targets

Fibrosis results from a response to injury that, although reparative in its origin, leads to excessive formation of fibrous connective tissue and scarring. This process causes structural damage, ultimately impairing organ function. Although the aetiology and epidemiology of fibrosis-related diseases — including pulmonary, cardiac, hepatic and kidney fibrosis — might differ, the fundamental mechanisms of fibrogenesis have common features across various organs and involve a complex fibrogenic niche where a dynamic interplay of cellular and molecular factors occurs[5]. An initial event leading to tissue injury triggers a cascade of cellular responses, resulting in the release of circulating factors and the activation of pro-fibrotic pathways. This effect, in turn, leads to the accumulation of ECM, tissue remodelling and scarring. Here, we consider the key contributors to the development of a fibrotic environment, highlighting the cellular and molecular interactions that drive fibrogenesis (Fig. 1).

Cellular response and fibroblast activation

Fibroblasts are cells of mesenchymal origin present in connective tissue, where they contribute to tissue integrity and flexibility. Myofibroblasts were historically considered to be a subfamily of fibroblasts with contractile properties and thought to be a central element of the fibrotic process as drivers of tissue remodelling and ECM organization[6]. However, the latest data indicate that myofibroblasts might have various sources, including not only resident fibroblasts but also pericytes, endothelial cells, bone-marrow-derived cells and epithelial cells[7]. Following tissue injury, cells undergo several changes, including loss of their original phenotype and the acquisition of myofibroblast-like characteristics such as the expression of α-smooth muscle actin (α-SMA)[6]. Single-cell RNA sequencing revealed distinct subpopulations of myofibroblasts in patients with CKD and showed that the primary cellular sources of myofibroblasts are subpopulations of fibroblasts and pericytes marked by a cessation of the cell cycle[8,9]. Thus, the main myofibroblast sources in the kidney are fibroblasts expressing platelet-derived growth factor receptor-α (PDGFRα) or PDGFRβ, maternally expressed 3 (MEG3), collectin subfamily member 11 (COLEC11) and CXC-chemokine ligand 12 (CXCL12), as well as pericytes expressing PDGFRβ, neurogenic locus notch homologue protein 3 (NOTCH3) and regulator of G protein signalling 5 (RGS5)[9]. Another study identified a fibroblast population at early stages of differentiation and with pro-inflammatory properties in patients with CKD[10]. These intermediate fibroblasts interact with macrophages to drive fibrosis progression in CKD[10]. Accordingly, when the insult is repetitive, injured cells fail to redifferentiate and this phenotypic transition leads to the abnormal release of pro-inflammatory and pro-fibrotic mediators, further contributing to tissue damage. Moreover, the complex interactions among these cells within the fibrotic niche, driven by paracrine signalling and cell–cell communication, influence the

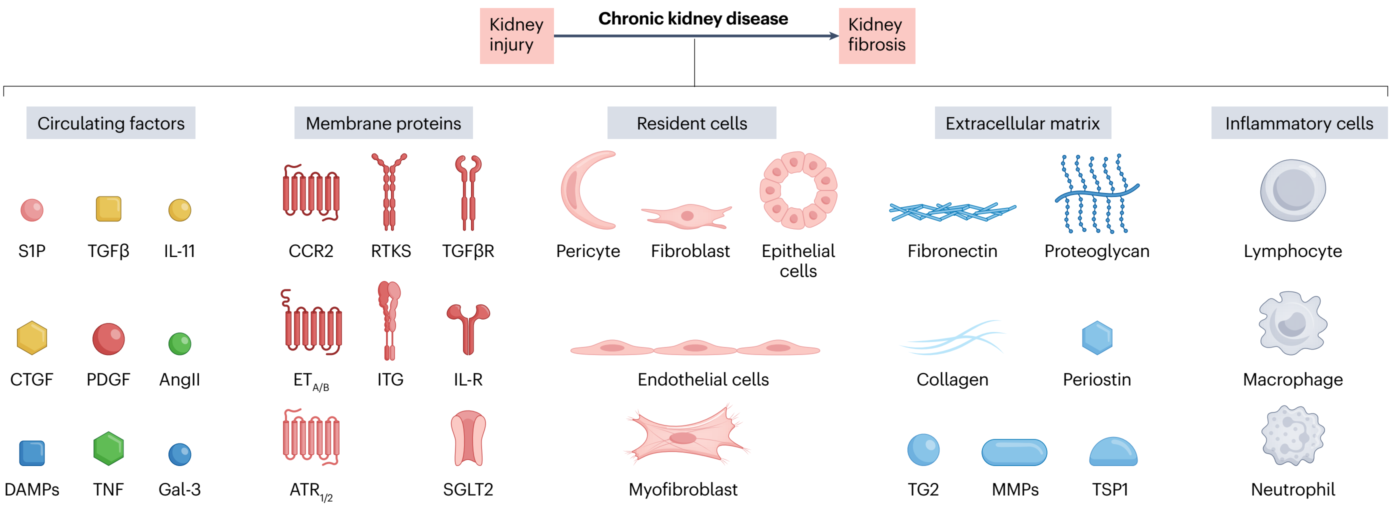

Fig. 1 | Major components of the kidney fibrogenic niche. Chronic kidney injury triggers a complex series of cellular events that result in kidney fibrosis. This process creates a fibrogenic environment characterized by inflammatory cell infiltration, receptor activation and cell signalling. In response to injury, cells express damage-associated molecular patterns (DAMPs), stress mediators such as angiotensin II (AngII), lipid mediators such as sphingosine 1-phosphate (S1P), pro-inflammatory cytokine and growth factors including galectin-3 (Gal-3), connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF), as well as cytokines such as tumour necrosis factor (TNF) and transforming growth factor-β (TGFβ). These circulating factors, in turn, lead to the recruitment of inflammatory cells and activate signalling through various receptor types, including tyrosine kinase receptors (RTKs), integrin receptors (ITG), CC-chemokine receptor 2 (CCR2), interleukin receptors (IL-R), endothelin A and B receptors (ET$_{A/B}$), and angiotensin receptors 1 and 2 (ATR$_{1/2}$). The niche is also enriched by resident cells – pericytes, fibroblasts, endothelial cells and epithelial cells – that can acquire a myofibroblast phenotype. Extracellular matrix (ECM) is a major structural element of the fibrotic niche that provides structural and biochemical support to cells. ECM comprises matricellular proteins such as transglutaminase 2 (TG2), periostin, matrix metalloproteinases (MMPs), thrombospondin 1 (TSP1), collagen and fibronectin.

progression of fibrosis. Endothelial dysfunction, for example, is closely linked with kidney tubular epithelial cell stress[11]. This dysfunction can also cause pericytes to detach and migrate into the kidney interstitial space, where they differentiate into myofibroblasts[12]. Epithelial cells also have a key role in the progression of fibrosis – after an initial insult, persistent injury leads to inadequate repair of kidney epithelial cells, which promotes abnormal ECM synthesis[13].

Immune cells and inflammation. Persistent inflammation, another key feature of CKD, is a major trigger of fibrogenesis. Although inflammation is necessary for tissue repair, it worsens fibrosis by maintaining myofibroblast activation and promoting ECM production[14]. The inflammatory repair process is often accompanied by amplification of tissue damage and disease progression, with the extent of immune cell infiltration closely related to the severity of kidney disease[15]. In the kidney, inflammation is linked to endothelial dysfunction as well as glomerular damage and tubular cell injury[16]. The infiltration and activation of immune cells such as macrophages, granulocytes and lymphocytes triggers the expression and release of cytokines and growth factors that contribute to ECM synthesis and accumulation[17].

The myeloid compartment consistently predominates after kidney injury. Macrophages are recruited to injured kidneys at an early stage and adopt a pro-inflammatory and pro-fibrotic phenotype, promoting kidney fibrosis by releasing galectin-3 (Gal-3) and metalloproteinases[18]. In the unilateral ureteral obstruction (UUO) mouse model, which results in accelerated tubular injury and interstitial fibrosis induced by obstructed renal flow, neutrophils are the most prevalent infiltrating immune cell[19]. Targeting macrophages and neutrophils in this model reduces tubular apoptosis and kidney fibrosis[19,20]. A similar pro-fibrotic role of macrophages and neutrophils has been described in lung and liver fibrosis[21,22]. T cells, B cells and natural killer cells also promote uncontrolled inflammation contributing to tissue scarring and delayed tissue repair in the liver, lung and kidney[23,24].

Circulating factors, receptors and signalling. The release of pro-fibrotic cytokines and growth factors, predominantly transforming growth factor-β (TGFβ), connective tissue growth factor (CTGF) and/or PDGF[25] triggers a complex cell-signalling network that involves pathways such as Janus kinase (JAK)–signal transducer and activator of transcription (STAT), phosphatidylinositol 3-kinase (PI3K)–protein kinase B (AKT) and Wnt–β-catenin pathways[26,27]. The TGFβ, CTGF and JAK–STAT pathways promote the synthesis of ECM components, such as collagen, and fibroblast activation[28]. The canonical signalling pathway of the major fibrotic cytokine, TGFβ, relies on the translocation of SMAD2, SMAD3 and SMAD4 into the nucleus to activate gene expression. However, activation of the TGFβ receptor (TGFβR) can initiate multiple signalling pathways shared with other receptors such as PDGFR[29]. For example, both PI3K–AKT and JAK–STAT pathways can be induced by activation of PDGFR and non-canonical TGFβR activation[30]. Similarly, the WNT–β-catenin pathway can be regulated by CTGF and the non-canonical TGFβ pathway[27]. This crosstalk between pathways can create feedback loops that intensify fibrogenesis. The overlapping and interconnected nature of these pathways contributes to the persistence of fibroblast activation and disease progression. Additionally, pro-inflammatory cytokines such as tumour necrosis factor (TNF) can also drive the activation and expression of pro-fibrotic cytokines, including TGFβ, which in turn can upregulate the expression of other pro-inflammatory cytokines, such as IL-11, and this crosstalk maintains and amplifies fibrosis[31,32].

Extracellular matrix formation. Disruption of the cellular dynamics and ECM remodelling have a pivotal role in shaping the fibrotic niche. These changes arise from increased expression, deposition and accumulation of structural ECM proteins[33]. The expression and organization of the ECM are tightly regulated by signalling molecules such as thrombospondin-1 (TSP1), TGFβ, PDGF and/or angiotensin II (AngII)[3,5,34]. The interaction between different components of ECM creates a complex network, and alterations in expression affect cellular interactions and tissue organization, thereby contributing to the formation of the fibrotic niche. Collagen is the primary structural protein of the ECM and its overproduction, particularly of type I and III collagen, leads to thickening and stiffening of the ECM[35]. The increased production of fibronectin serves as a scaffold for collagen deposition[36]. Activated synthesis of other ECM proteins such as proteoglycans, laminin, fibrin, thrombospondins and periostin enhances abnormal ECM accumulation and further contributes to the progression of fibrosis[37]. Increased ECM accumulation might also result from reduced ECM degradation driven by an imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). MMPs are responsible for ECM breakdown, and their activity is tightly regulated by TIMPs[38]. Additionally, enzymes such as transglutaminases can facilitate cross-linking between ECM component proteins, enhancing their resistance against protease degradation[39].

The mechanisms mentioned above that promote changes in ECM structure and regulation contribute to the persistence and progression of fibrosis, and ultimately disrupt tissue structure and function. The intricate mechanisms involved complicate the development of targeted therapies against fibrosis.

Therapies targeting pro-fibrotic pathways

Different strategies can be used to target fibrogenic niche formation and aberrant ECM accumulation in the kidney directly. Here, we examine kidney fibrosis clinical trials that have been discontinued or failed to show a benefit, followed by a discussion of successful anti-fibrotic treatments in other organs that might be applicable to the kidneys. Of note, nephroprotective drugs, which are aimed at slowing the progression of CKD, regardless of disease aetiology and its underlying mechanisms, can also target the fibrogenic niche. The main purpose of several nephroprotective drugs is to control hypertension and/or diabetes and their anti-fibrotic effectiveness is probably because their targets, which include vasoconstrictors such as AngII, endothelin-1 or aldosterone, also directly promote fibrogenesis through the activation of their receptors[3,40,41] (Fig. 2). Although the progression of kidney fibrosis cannot be easily assessed through histology as ethical principles prohibit repetitive biopsies, and reliable and non-invasive methods for measuring kidney fibrosis are currently lacking, the protection of kidney function mediated by these drugs is also probably accompanied by preservation of kidney structure.

Unsuccessful therapeutic interventions

Several therapies have been deployed to target kidney fibrosis but, despite initial promising results, most failed to generate a positive therapeutic outcome (Table 1). Most studies have targeted TGFβ signalling, which is a central mediator of fibrosis, with a pleiotropic role in various biological processes. Excessive TGFβ signalling leads to uncontrolled tissue scarring and induces accumulation of ECM components, resulting in tissue dysfunction[42]. A range of therapeutic approaches have been developed to inhibit TGFβ-induced fibrosis: scavengers of TGFβ (decorin), neutralizing antibodies against circulating TGFβ, monoclonal antibodies against TGFβR, soluble TGFβR traps and

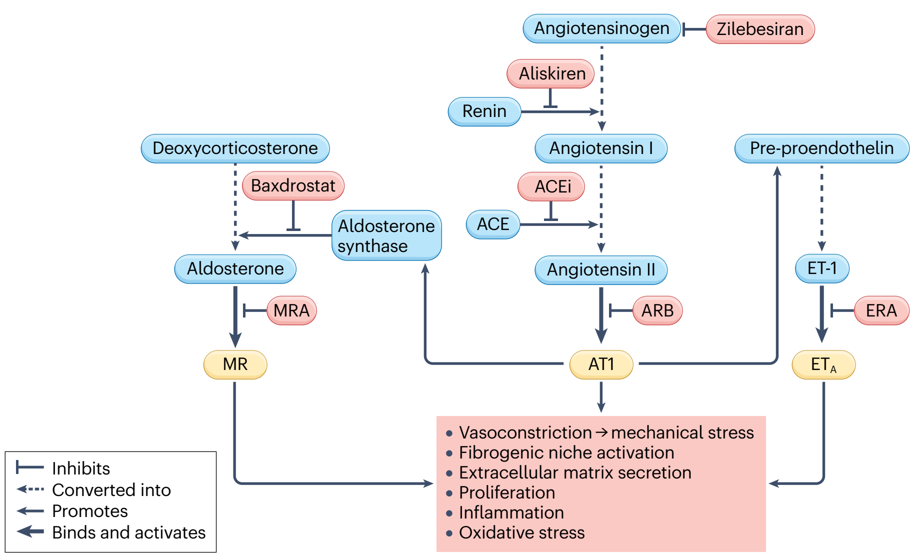

Fig. 2 | Targeting RAAS and endothelin activation. The figure illustrates the biogenesis pathways of angiotensin II, aldosterone and endothelin-1 (ET-1) and their effects on the kidney fibrogenic niche. Angiotensin II is produced from angiotensinogen via renin, angiotensin I and angiotensin-converting enzyme (ACE). Angiotensin II promotes aldosterone release from the adrenal cortex and pre-proendothelin cleavage into ET-1. These molecules increase glomerular mechanical burden through vasoconstriction, and increased water and sodium retention. In addition to this mechanical burden, the interplay of angiotensin II, aldosterone and ET-1 fosters a pro-fibrotic environment in the kidneys, exacerbating kidney injury and dysfunction. Multitargeted pharmacological blockade of the renin–angiotensin–aldosterone system (RAAS) and the endothelin system has proven highly effective in preventing kidney fibrosis progression. ACEi, ACE inhibitor; MR, mineralocorticoid receptor; MRA, MR antagonist; AT1, angiotensin II receptor type 1; ARB, angiotensin receptor blocker; ERA, ET_A-selective endothelin receptor antagonists; ET_A, endothelin A receptor.

Table 1 | Discontinued clinical trials of anti-fibrotic treatments in CKD

Target	Drug name	Disease	Clinical trial	Phase and status	Outcome
TGFβ	Fresolimumab	FSGS	NCT01665391	Phase II, completed	No reduction in proteinuria, no change in GFR
	LY2382770	DKD	NCT01113801	Phase II, terminated	No difference in serum creatinine
CTGF	Pamrevlumab	IPF	NCT04419558 NCT03955146	Phase III, terminated	Ineffective preservation of lung function
	FG-3019	DKD	NCT00913393	Phase II, terminated	Terminated for business purposes
		FSGS	NCT00782561	Phase I, terminated	Terminated
NRF2	Bardoloxone methyl	CKD	NCT03749447 (EAGLE)	Phase III, terminated	Not FDA-approved, lack of evidence of efficiency, risk of hepatotoxicity, heart failure and death from cardiovascular events
		DKD	NCT03550443 (AYAME)	Phase III, terminated	
		ADPKD	NCT03918447 (FALCON)	Phase III, terminated	
		Alport syndrome	NCT03019185 (CARDINAL)	Phase II and III, completed	
miR-21	Lademirsen	Alport syndrome	NCT02855268	Phase II, terminated	Interrupted for lack of eGFR improvement
Integrin αvβ6	STX-100 (BG-00011)	CKD	NCT00878761	Phase II, withdrawn	Discontinued for unknown reasons

ADPKD, autosomal-dominant polycystic kidney disease; CKD, chronic kidney disease; CTGF, connective tissue growth factor; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IPF, idiopathic pulmonary fibrosis; miR-21, micro-RNA 21; TGFβ, transforming growth factor-β.

modulators of TGFβ signalling (bone morphogenic protein 7 (BMP7))[43]. Some approaches, such as the administration of decorin or BMP7 led to impressive results in preclinical studies[44,45], but their long-term use caused severe undesirable effects that preclude their use in patients with CKD. Similarly, therapies blocking TGFβ directly, such as fresolimumab and LY2382770, inhibited fibrosis efficiently in preclinical CKD, but failed to show benefit in clinical trials[46,47] (Table 1). Other therapeutic strategies targeting CTGF, which is a downstream effector of TGFβ (pamrevlumab, FG-3019), also failed to show substantial benefit or their trials were terminated prematurely (Table 1). Adverse events observed after TGFβ inhibition include inflammation, toxicity and/or cytokine release syndrome[32,48]. These distinct and undesirable effects induced by TGFβ inhibition might partly explain the lack of positive clinical results. Alternative strategies have thus been established that go beyond targeting TGFβ, notably by targeting the oxidative stress that promotes the release of pro-fibrotic mediators and the persistence of fibrosis. For example, bardoxolone-methyl, which is a potent activator of nuclear transcription factor NRF2-mediated anti-oxidant and anti-fibrotic effects, improved estimated glomerular filtration rate (eGFR) in people with CKD associated with type 2 diabetes[49,50]. However, in phase III studies (Table 1) bardoxolone not only failed to slow eGFR decline but also increased albuminuria and the risk of cardiovascular events[51,52]. Alternative approaches, including the inhibition of small non-coding RNAs involved in kidney disease and fibrosis[53,54], such as the miR-21 antagomir (lademirsen), have not delivered the expected outcomes in patients with Alport syndrome either (Table 1).

Finally, STX-100 (also known as BG00011), which is a humanized antibody designed to target and inhibit αvβ6 cell surface receptors involved in the release of active TGFβ[55], was effective in blocking fibrogenesis in a phase II study (NCT01371305) of a small population of patients with idiopathic pulmonary fibrosis (IPF)[56]. However, a preclinical study for the prevention of chronic allograft fibrosis indicated that blocking αvβ6 increased the risk of acute kidney rejection[57], and a trial for chronic allograft dysfunction was withdrawn for unknown reasons[58].

These disappointing results raise questions about why the success story of preclinical studies has not been translatable to patients with CKD, and why anti-fibrotic treatments that are effective in patients with fibrosis in other tissues, such as the lungs and liver, have failed when applied to kidney fibrosis.

Regarding the species difference, the complexity of CKD in humans cannot be fully replicated in animal models and substantial differences exist in the underlying disease mechanisms between species. Moreover, animal studies are often of short duration, which limits the ability to assess potential side and off-target effects. Complications related to the pharmacokinetics, bioavailability and administration of these agents have also hampered their success. Furthermore, therapies in preclinical studies are typically administered at an early stage of disease, before disease-driven alterations become irreversible, and they usually involve young animals, whereas therapies in clinical trials are often assessed in older patients with advanced disease.

Regarding the tissue difference, loss of kidney function is generally detected late and therapies are thus initiated in advanced stages of CKD, when the damage might be irreversible, thus reducing the window for effective intervention. Identifying biomarkers that allow early disease detection might yield better results, as the progression of kidney fibrosis is generally asymptomatic. The lungs and liver are more accessible for biopsies and imaging, thus facilitating the monitoring of disease progression and response to treatments. Furthermore, the kidney is probably the tissue with the greatest cellular diversity in the body, with more than 50 different cell types, which leads to complex cellular interactions and distinct pathophysiological processes in different compartments, such as glomerulosclerosis, tubular interstitial fibrosis or vascular sclerosis, thus increasing the risk of incomplete and ineffective treatment. An additional complication arises from the signalling pathway overlap between fibrosis and wound healing. Chronic inactivation of these pathways can therefore interfere with repair and healing of other tissues.

Despite several unsuccessful interventions, therapies targeting fibrosis are continually emerging. The main reason for this persistence is that advancing mechanistic knowledge and technological innovations in drug delivery (discussed further below) might enable the specific targeting of kidney fibrosis without secondary complications.

Ongoing clinical trials of anti-fibrotic treatments

Most current strategies focus on indirectly modulating the different actions of TGFβ to achieve better therapeutic results and avoid toxic side effects. In these trials, priority is given to pulmonary or hepatic fibrosis, for the reasons explained above (easier monitoring of disease progression and response to treatments). Regardless of the challenge posed by kidney complexity, the success of pulmonary and hepatic therapies might still provide clues to the treatment of kidney fibrosis (Table 2 and Fig. 3).

Targeting the TGFβ pathway with pirfenidone. Described as an immunosuppressive with anti-oxidant properties, pirfenidone has anti-fibrotic effects in lung, kidney and liver through a mechanism involving downregulation of TGFβ expression that is not yet fully understood. Pirfenidone seems to exert an anti-fibrotic action by inhibiting SMAD2 and/or SMAD3 phosphorylation[59], and retaining TGFβ in a latent form by inhibiting furin, a proteolytic enzyme involved in TGFβ maturation[60]. Pirfenidone administration decreased mRNA expression of TGFβ and levels of type I and VI collagen, attenuated fibrosis and kidney damage, and increased glomerular filtration in experimental models of kidney disease[61].

Pirfenidone medication is approved for the treatment of IPF, with efficacy in reducing lung function decline and disease progression[62]. The

Table 2 | Ongoing clinical trials with anti-fibrotic drugs

Target	Drug name	Disease	Clinical trial	Phase and status	Outcome
TGFβ pathway					
TGFβ, SMAD3	Pirfenidone	IPF	NCT00660238	Marketed, completed	Reduced decline of lung function and improved survival
		CKD	NCT04258397	Phase II, recruiting	NA
TGFβ, p38, MAPK	Hydronidone	Liver fibrosis	NCT05115942	Phase III, completed	NA
TGFβ, SMAD2, 3 and 4, NF-κB	Pentoxifylline	DKD	NCT03625648	Phase IV, recruiting	NA
		DKD	NCT03664414	Phase IV, unknown	NA
Tyrosine kinase pathway					
RTKs (PDGFRs, FGFRs, VEGFRs)	Nintedanib	IPF	NCT02598193	Marketed, completed	Reduced progression of fibrosis
JAK1 and JAK2	Ruxolitinib	Myelofibrosis	NCT2386800	Marketed, completed	Improved survival
	Baricitinib	FSGS and DKD	NCT05237388	Phase III, recruiting	NA
Receptors					
S1P and S1PR	Fingolimod	IFTA Kidney transplantation	NCT05285878	Phase II, active	NA
GLP1R	Exenatide	DKD	NCT02690883	Phase IV, completed	Albuminuria reduction
	Dulaglutide	DKD	NCT05218915	Phase IV, recruiting	NA
	Semaglutide	CKD	NCT04865770	Phase III, recruiting	NA
CCR2	DMX-200	FSGS	NCT05183646	Phase III, recruiting	NA
THRβ	Resmetirom	NASH	NCT03900429	Phase III, active	NA
Cytokines					
Galectin-3	Belapectin	NASH	NCT04365868	Phase II and III, active	NA
	GB1211	IPF	NCT03832946	Phase II, recruiting	NA
	GCS-100	DKD	NCT02312050	Phase II, unknown	NA
IL-11	BI-765423	Safety assessment for fibrotic disease	NCT05658107	Phase I, active	NA
Epigenetic					
BET	Apabetalone	Pulmonary arterial hypertension	NCT04915300	Phase II, not yet recruiting	NA

ADPKD, autosomal-dominant polycystic kidney disease; BET, bromodomain and extraterminal; CCR2, CC-chemokine receptor 2; CKD, chronic kidney disease; DKD, diabetic kidney disease; FGFR, fibroblast growth factor receptor; FSGS, focal segmental glomerulosclerosis; GLP1R, glucagon-like peptide 1 receptor; IFTA, interstitial fibrosis and tubular atrophy; IPF, idiopathic pulmonary fibrosis; NA, not available; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor-κB; PDGFR, platelet-derived growth factor receptor; RTK, receptor tyrosine kinase; S1PR, sphingosine 1-phosphate receptor; TGFβ, transforming growth factor-β; THRβ, thyroid hormone receptor-β; VEGFR, vascular endothelial growth factor receptor.

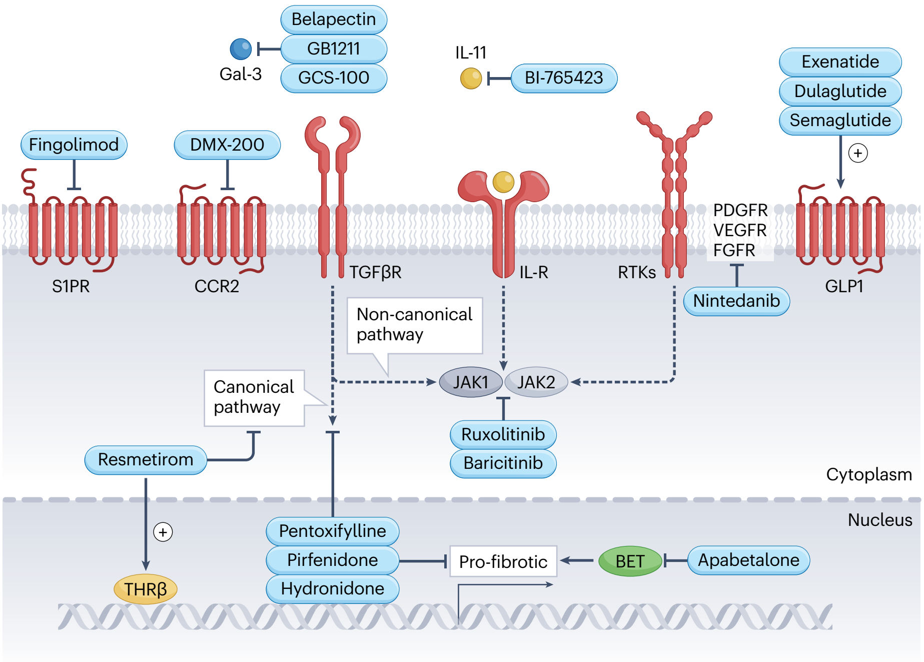

Fig. 3 | Summary of promising anti-fibrotic drugs. Targeting JAK–STAT signalling affects pathways involving the non-canonical transforming growth factor-β receptor (TGFβR), interleukin receptors (IL-R) and tyrosine kinase-β receptors (RTKs) such as platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor (VEGFR) and fibroblast growth factor (FGFR). Pro-fibrotic mediators and receptors can be regulated by drugs inhibiting the canonical and non-canonical TGFβ signalling pathways, and by targeting epigenetic modulation mediated by bromodomain and extraterminal (BET) family proteins. Inhibition of CC-chemokine receptor 2 (CCR2), sphingosine 1-phosphate receptor (S1PR), IL-11 and galectin-3 (Gal-3), as well as the use of agonists that activate thyroid hormone receptor-β (THRβ) and glucagon-like peptide 1 receptor (GLP1R) can also have an anti-fibrotic effect.

exact protective mechanisms of action involved are poorly understood, but are thought to reduce pulmonary inflammation and fibrosis.

In CKD, only a few clinical studies have been performed, all of which showed a positive effect. Thus, in an open-label, single-centre pilot study in patients with focal segmental glomerulosclerosis (FSGS), pirfenidone slowed the eGFR decline rate[63]. In a randomized study involving participants with diabetic nephropathy, patients received either placebo or different doses of pirfenidone. After 1 year, mean eGFR increased, and the number of patients requiring haemodialysis was significantly lower in the group receiving a low dose of pirfenidone compared with the group receiving placebo or a high dose of pirfenidone. However, no significant differences were observed in urinary excretion of TGFβ and albumin-to-creatinine ratio[64]. Nevertheless, both studies had important limitations – short duration and small sample sizes, which limits the generalization of the results to a larger population, and lack of appropriate tolerability and safety considerations.

A larger ongoing clinical trial for pirfenidone with 200 participants (TOP-CKD, Table 2) should provide more accurate information on the effects of pirfenidone therapy and a better evaluation of the reported side effects (gastrointestinal symptoms, skin reactions and liver enzyme elevations)[65].

Targeting the TGFβ pathway with hydronidone. Hydronidone is structurally related to pirfenidone and also downregulates the TGFβ signalling pathway, probably via SMAD7-mediated degradation of TGFβR1 (ref. 66). In a phase II trial for treatment of liver fibrosis associated with chronic hepatitis B, hydronidone combined with entecavir reduced liver fibrosis and improved liver histology[67]. A phase III trial was completed for chronic hepatitis B (Table 2) at the end of 2024, but the results have not yet been published. If the results are positive, they will serve as the basis for testing hydronidone as a treatment for kidney fibrosis.

Targeting the TGFβ pathway with pentoxifylline. Pentoxifylline belongs to a class of vasodilators with additional anti-inflammatory and potential anti-fibrotic properties through inhibition of cell proliferation and ECM production[68,69]. Used in combination with AngII type 1 (AT1) receptor antagonists, pentoxifylline had the most effective anti-inflammatory and anti-albuminuric effects in diabetic nephropathy[70,71] (Table 2).

Targeting tyrosine kinase activation with nintedanib. Nintedanib is a triple tyrosine kinase receptor inhibitor targeting multiple pathways involved in fibrosis, including those involving the vascular endothelial growth factor receptor (VEGFR), PDGFR and the fibroblast growth factor receptor (FGFR). Effective in treating IPF, nintedanib shows promise as a potential treatment for fibrosis in other organs. Nintedanib delayed fibrosis progression in the UUO model and in a model of acute-to-chronic kidney injury induced by high doses of folic acid[72,73], as well as significantly reducing fibrosis and cyst growth in a model of autosomal-dominant polycystic kidney disease[74]. Minimal side effects were observed in patients with IPF and severe CKD (creatinine clearance <30 ml/min)[75]. However, microangiopathy and nephrotic-range proteinuria with kidney function impairment have also been reported in a few cases[76,77]. Considering the potential side effects, further studies that include monitoring of proteinuria and assessment of histological improvement are needed to better evaluate the role of nintedanib as a potential anti-fibrotic agent in CKD.

Targeting tyrosine pathways with ruxolitinib and baricitinib. JAK1 and JAK2 are involved in the development and progression of different types of kidney disease[78]. Data based on experimental models of CKD suggest a potential therapeutic benefit of inhibiting JAK signalling[78]. Ruxolitinib, which is a selective inhibitor of JAK1 and JAK2, is approved for targeting BM fibrosis in myelofibrosis[79] (Table 2). Fedratinib, which is a selective JAK2 inhibitor and is approved as an alternative treatment for patients with ruxolitinib-resistant myelofibrosis, could also be considered for CKD[80]. Baricitinib, another JAK1 and JAK2 inhibitor, reduced disease activity in systemic lupus erythematosus in phase II trials. However, the complementary phase III trial SLE-BRAVE-II, with a larger cohort and longer duration, failed to replicate the efficacy outcomes initially observed[81,82]. Promising results were observed with baricitinib in a randomized study, which showed a 40% decrease in albuminuria after 3 months and 6 months in patients with diabetic nephropathy[83]. A phase III study is underway for FSGS (Table 2).

Activating GLP1R. Activation of glucagon-like peptide 1 receptor (GLP1R) reduced albuminuria and prevented loss of kidney function[84–86]. The exact mechanisms of action of GLPR1 agonists are complex and might involve the downregulation of inflammatory and fibrogenic proteins[87]. In addition to having a beneficial effect on the reduction of albuminuria, these agonists protected patients with CKD and a high cardiovascular risk, and no significant adverse events have been reported[84]. Further cardiovascular and kidney benefits have been observed when a GLP1R agonist was combined with a sodium–glucose co-transporter 2 (SGLT2) inhibitor[88]. More studies are currently underway in CKD and DKD using exenatide, dulaglutide and semaglutide (Table 2).

Activating THRβ receptor. Thyroid hormone-β (THRβ) receptors are abundantly expressed in liver and kidney[89]. These receptors might influence TGFβ signalling through direct interaction or by binding promoter regions of TGFβ[90]. Results from patients with NASH suggest that THRβ agonist treatment (resmetirom) improved liver fibrosis, reverting it by at least one disease stage[91]. Given that NASH and CKD share several common triggers, it will be interesting to test this therapy in kidney fibrosis.

Targeting immunoreceptors. CC-chemokine receptor 2 (CCR2) has a crucial role in the recruitment of monocytes and macrophages to sites of injury, and is closely associated with fibroblast activation and ECM deposition[17,92]. The adjuvant therapy DMX-200, which combines a selective CCR2 antagonist and an AT1 antagonist, reduced proteinuria in patients with FSGS in an early-phase clinical trial[93]. This dual approach provides a multifaceted anti-fibrotic effect not only by attenuating inflammation but also by inhibiting the RAAS. Currently, DMX200 is in phase III clinical trials for the treatment of FSGS (Table 2).

The sphingosine 1-phosphate receptor (S1PR) is also a crucial regulator of inflammation and fibrosis. In response to the bioactive lipid S1P, S1PR1 signalling leads to the recruitment and activation of immune cells, as well as the migration and proliferation of fibroblasts, thereby promoting fibrosis[94]. S1PR modulators, such as fingolimod, are under investigation for treating interstitial fibrosis and tubular atrophy in kidney transplantation (Table 2).

Targeting Gal-3. Galectin-3 (Gal-3) is a pro-inflammatory and pro-fibrotic cytokine that is elevated in AKI and CKD, and has been associated with kidney fibrosis and kidney disease progression[95,96]. The potential of Gal-3 inhibitors to mitigate fibrosis and CKD progression has been evaluated in preclinical models of hypertensive nephropathy[97]. Gal-3 inhibition led to reductions in proteinuria, plasma creatinine levels, inflammation and kidney damage. A study is currently investigating the use of a Gal-3 inhibitor as a potential treatment for CKD (Table 2).

Targeting IL-11. IL-11 is one of the most upregulated genes in people with kidney failure compared with healthy individuals[98,99]. In response to pro-fibrotic stimuli such as TGFβ, resident fibroblasts secrete IL-11, which further enhances fibrosis[100]. Evidence from preclinical studies in UUO, folic acid and Alport models suggests that targeting IL-11 has the potential to stop and reverse fibrosis, with the added benefit of restoring blocked endogenous regeneration in the kidneys[32,101,102]. Clinical trials are underway to assess the safety of this treatment and to explore its use in pulmonary fibrosis. If the effectiveness of IL-11 inhibition is confirmed, it would pave the way for its testing in kidney fibrosis.

Targeting epigenetic modulation with BET. Bromodomain and extraterminal (BET) family proteins are epigenetic readers capable of modulating the expression of a wide range of genes involved in inflammation and fibrosis[103]. BETs inhibitors gained interest as a potential therapy in fibrosis because they slow aberrant expression of pro-inflammatory and pro-fibrotic genes. The use of the BET inhibitor apabetalone in patients with CKD had a favourable effect on eGFR and the alkaline phosphatase profile, as well as a cardioprotective effect[104,105]. However, clinical testing in Fabry disease was withdrawn owing to changes in the priorities of the company[106]. Further studies are required to confirm its efficacy, safety and optimal use in the treatment of kidney fibrosis.

Blocking vasoconstrictor systems

Hypertension is both a hallmark and a major risk factor for CKD — up to 85% of people with CKD have elevated blood pressure. Hypertension and high mechanical stress on the glomerulus are associated with proteinuria and glomerulosclerosis. Large randomized trials have established that tight control of blood pressure is a key element in reducing mortality in people with CKD[107]. Among antihypertensive medications, those targeting the RAAS have been shown to be effective in preserving the kidney structure and function, and preventing the progression of CKD, particularly in patients with proteinuria[108]. Interestingly, in this population, the outcome seems to surpass the effect predicted by blood pressure reduction alone, suggesting a specific impact of the RAAS inhibition on CKD progression and kidney fibrosis.

Angiotensin-converting inhibitors and angiotensin receptor blockers. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are beneficial in almost all types of CKD and are therefore recommended as first-line antihypertensive and antiproteinuric drugs. The superiority of ACE inhibitors and ARBs compared with placebo and alternative antihypertensive treatments was convincingly demonstrated in a meta-analysis[109] (Table 3).

The antiproteinuric effect of ACE inhibitors and ARBs is probably mediated by the relaxation of afferent and efferent arterioles in the glomeruli and the subsequent decrease in intraglomerular pressure. This outcome can be further enhanced through synergistic volume depletion induced by diuretics[110]. Although this haemodynamic effect might increase the risk of hypovolaemia-induced AKI, even in patients with low eGFR, this risk does not outweigh the benefit of ACE inhibitors and ARBs[111,112].

As mentioned above, ACE inhibitor and ARB-induced nephroprotection, independently of haemodynamics, probably relies on the direct action of AngII on the fibrogenic niche. Preclinical studies showed that binding of AngII to the AT1 receptor activates several cellular pathways related to fibrogenesis[34,113]. Briefly, AngII enhances the production of reactive oxygen species, impairs cell-cycle regulators by affecting cyclin pathways, activates the TGFβ–SMAD pathway,

Table 3 | Clinical trials showing improved eGFR and/or proteinuria in CKD

Intervention	Population	Main results	Ref.
Blocking vasoconstrictor systems			
Blood pressure control SBP (140 versus 120 mmHg)	CKD; 2,646 participants	Reduced mortality and cardiovascular events, no effect on kidney criteria (eGFR)	107
ACE inhibitors and ARBs (network meta-analysis)	42 clinical trials; 42,319 participants	Positive effect on composite kidney criteria: serum creatinine doubling, 50% GFR decline or kidney failure: OR 0.54 (CI 0.41–0.73), reduced all-cause mortality and cardiovascular events	108
Finerenone versus placebo[a]	Type 2 diabetes; 5,734 + 7,437 participants	Positive effect on composite kidney criteria: sustained >57% decrease in eGFR and renal death: HR 0.77 (CI 0.67–0.88), positive effect on main cardiovascular events	121
Sparsentan 800 mg versus irbesartan 300 mg.	FSGS; 371 participants	Negative on main evaluation criteria: eGFR slope difference at week 108, positive effect on proteinuria reduction criteria	130
Sparsentan 400 mg versus irbesartan 300 mg.	IgA nephropathy; 406 participants	Positive effect on main kidney criteria: slower eGFR reduction (slope difference week 6–110 was 1.1 ml/min/1.73 m^2/year), proteinuria reduction week 0–110, no benefit reported: kidney failure, 40% eGFR reduction or mortality	129
Zibotentan (1.5 mg or 0.25 mg) or placebo[b]	CKD; 447 participants (60% with type 2 diabetes)	Positive effect on proteinuria reduction: log-transformed UACR change from baseline to week 12 compared with placebo (1.5 mg: −33.7% (CI −42.5 to −23.5); 0.25 mg: −27% (CI −38.4 to −13.6)), good tolerance (fluid overload)	131
Atrasentan 0.75 mg versus placebo[a]	Type 2 diabetes; 2,648 participants	Positive effect on main kidney criteria: time to serum creatinine doubling or kidney failure, or death from kidney failure: HR 0.65 (CI 0.49–0.88), time to 50% serum creatinine increase: HR 0.73 (CI 0.55–0.98)	128
SGLT2 inhibitor in addition to ACE inhibitor and/or ARB			
Canagliflozin 100 mg versus placebo[a]	Type 2 diabetes; 4,401 participants	Positive effect on main kidney criteria: kidney failure, serum creatinine doubling or death of renal cause; HR 0.66 (CI 0.53–0.81), reduced all-cause mortality and cardiovascular events	132
Dapagliflozin 10 mg versus placebo[a]	CKD; 4,304 participants (68% with type 2 diabetes)	Positive effect on primary kidney end point: time to composite (50% eGFR decline; kidney failure; death from renal or cardiovascular cause), HR 0.61 (CI 0.51–0.72), reduced main cardiovascular events, including mortality	133
Empagliflozin 10 mg versus placebo[a]	CKD; 6,609 participants (44% with type 2 diabetes)	Positive effect on main kidney criteria: kidney failure or eGFR <10 ml/min/1.73 m^2 or 40% eGFR decrease or death from a renal cause. HR 0.72 (CI 0.64–0.82), reduced hospitalization rate, but no benefit on heart failure hospitalization or cardiovascular death	134

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio; OR, odds ratio; SBP, systolic blood pressure; SGLT2, sodium–glucose co-transporter 2; UACR, urinary albumin-to-creatinine ratio. [a]In addition to maximum dose of ACE inhibitor and/or ARB. [b]In addition to dapagliflozin 10 mg and maximum dose of ACE inhibitor and/or ARB.

transactivates EGFR and PDGFR signalling, and stimulates fibrillar collagen and ECM protein synthesis. AngII can also induce the expression of several additional pro-fibrotic and pro-inflammatory genes such as aldosterone or endothelin-1 (ET-1).

Given its numerous pleiotropic deleterious effects, investigators have continued to develop treatments to prevent the formation of AngII, despite the effectiveness of ACE inhibitors and ARBs. Zilebesiran is a new drug based on RNA interference that targets the hepatic synthesis of angiotensinogen. A single subcutaneous injection of zilebesiran was sufficient to produce a sustained, safe and dose-dependent decrease in serum angiotensinogen and blood pressure for several months[114,115]. Two ongoing trials of zilebesiran in patients with uncontrolled hypertension despite the use of 2–4 antihypertensive medications and at high cardiovascular risk or advanced CKD, will inform the use of this new treatment as a nephroprotective therapy[116,117].

Mineralocorticoid receptor inhibition. Aldosterone is the main mineralocorticoid hormone. Its concentration is regulated by kalaemia, sodium and extracellular depletion, and it is the end product of the RAAS. The main target of aldosterone is the collecting duct, but its receptor, the mineralocorticoid receptor (MR), is almost ubiquitous and expressed in all kidney cells involved in the fibrogenic niche, such as podocytes, myeloid cells, fibroblasts, T cells and vascular smooth cells.

Cell-specific MR genetic deletion clarified the different pro-fibrotic effects of MR activation. For example, activation of MR in podocytes increases autophagy and induces downregulation of nephrin, podocin, podoplanin and podocalyxin[118]. MR activation in fibroblasts participates in CKD-associated kidney remodelling via fibronectin secretion, and MR modulates the response of fibroblasts to PDGF and CTGF. In endothelial cells, aldosterone increases the expression of pro-fibrotic mediators such as ICAM-1, VCAM-1, E-selectin and MCP-1. Aldosterone can also stimulate RAC1 activation, increase oxidative damage and promote endothelial dysfunction via impaired endothelial nitric oxide synthase (eNOS) phosphorylation[118].

The demonstration that AngII is not the sole regulator of aldosterone and that MR can be activated independently of aldosterone argues for additional MR blockade, in addition to the use of ACE inhibitors and ARBs[118]. Although MR inhibitors have gained a place of choice as anti-fibrotic drugs in chronic cardiac dysfunction and several trials with the first generation of MR antagonists (MRAs) — spironolactone and eplerenone — showed an anti-proteinuric effect in addition to that of AngII blockade[119,120], their use in patients with CKD remained limited because of poor tolerance and undesirable side effects such as hyperkalaemia or cross-reactions with other steroid hormones.

However, MR inhibition resurged as a therapeutic strategy in CKD after the development of non-steroidal MRAs such as exaserenone, aperenone and finerenone. Exaserenone is authorized in Japan as an antihypertensive drug. Following two major positive trials in patients with type 2 diabetes (Table 3), finerenone was approved by the FDA and was included in the 2024 KDIGO recommendations as a nephroprotective agent in people with diabetes[121,122]. No scientific rationale suggests that this protective effect should be limited to diabetic nephropathy and further development of this treatment in patients with CKD is expected, as supported by a preclinical study in a murine model of Alport disease[123]. The anti-aldosterone drug array will be reinforced by the aldosterone synthase inhibitor baxdrostat, which in a phase II trial induced a dose-dependent decrease in blood pressure in patients with treatment-resistant hypertension[124].

Endothelin blockade. The endothelin system shares several downstream effects with RAAS. ET-1, the predominant endothelin isoform expressed in the renal and cardiovascular systems, is the most potent vasoconstrictor known in humans. The detrimental effects of ET on renal haemodynamics, sodium and water homeostasis, and the acid–base balance are well established[125]. AngII can also induce ET-1 synthesis in kidney endothelial and mesangial cells, and endothelin A receptor (ET_A) antagonists attenuate the hypertensive and fibrogenic effects of AngII (Fig. 2). A link between the fibrogenic niche and ET overactivation has been demonstrated in podocytes, mesangial cells, tubular epithelial cells and in the renal vasculature. Inhibition of ET-1 can reduce fibrogenesis in animal models of hypertensive nephropathy, diabetes, IgA nephropathy, lupus nephritis, sickle cell disease and FSGS, illustrating the broad spectrum of potential applications for this therapy[126].

The use of the first ET inhibitors was hampered by deleterious side effects, including liver toxicity and risk of fluid overload[127]. Refining the specificity of their action, better patient selection and appropriate management of fluid overload enabled the clinical emergence of three new ET_A antagonists for the prevention of CKD – sparsentan, zibotentan and atrasentan. Use of these ET_A antagonists provided an additional benefit to that provided by ACE inhibitors and ARBs in phase III trials in various types of CKD, such as diabetic nephropathy, IgA nephropathy and FSGS[128–130] (Table 3). In a phase IIb trial in patients with proteinuria, the co-administration of zibotentan and dapagliflozin, alongside ACE inhibitor or ARB therapy, resulted in a further reduction in albuminuria, regardless of the underlying CKD aetiology[131]. Ongoing phase III trials will be decisive in informing the use of ET-1 blockers as nephroprotective agents.

SGLT2 inhibitors

Unlike RAAS and ET inhibitors, the impressive impact of SGLT2 inhibitors on CKD progression was less expected. Nevertheless, these drugs, which were initially developed against diabetes, slow down CKD progression, and reduce morbidity and mortality in people with CKD[132–134] (Table 3). Based on these trials, 2024 KDIGO recommendations state that SGLT2 inhibitors should be used in all people with eGFR > 20 mL/min/1.73m^2 and type 2 diabetes, or albuminuria > 200 mg/g or heart failure (grade 1 A). This drug class is also recommended for people without diabetes or proteinuria with an eGFR 20–45 mL/min/1.73m^2 (grade 2B), giving SGLT2 inhibitors a place almost as central as that of ACE inhibitors and ARBs as nephroprotective agents[122].

The mechanisms explaining the remarkable clinical success of SGLT2 inhibitors are not yet fully understood (Fig. 4). As with RAAS and ET inhibitors, part of the efficiency of SGLT2 inhibitors derives from improvements in glomerular haemodynamics and increased natriuresis[135]. SGLT2 inhibitors reduce inflammation, fibrosis and protect kidney function in several models of kidney disease[136]. Moreover, SGLT2 inhibition reduces the release of pro-inflammatory cytokines such as IL-1α, IL1-β, IL-18 and TNF, and downregulates major pro-inflammatory pathways such as the nuclear factor-κB (NF-κB), TGFβ or STAT pathways. SGLT2 inhibition is also proposed to activate AMPK-related pathways, inducing beneficial metabolic reprogramming[137]. A large multiomics-based study in rodents demonstrated the broad spectrum of action of SGLT2 inhibition on many different apical tubular transporters, suggesting that the impact of these drugs on proximal tubular transport goes well beyond its effects on glucose and sodium transport[138]. Interestingly, this study identified an additional unexpected target of SGLT2 inhibition – the microbiota. SGLT2 inhibition altered faecal fermentation and modified the formation of microbiota-related uraemic toxins such as *p*-cresol[138].

Diet and lifestyle

Low-protein diets are recommended by most international guidelines to slow the progression of CKD[122]. Interestingly, these diets seem to share several protective mechanisms with SGLT2 inhibitors – reduction of intraglomerular pressure[139] and altered synthesis of microbiota-related uraemic toxins. One study indicated that lowering dietary aromatic amino acids improved kidney function, as evidenced by reduced serum

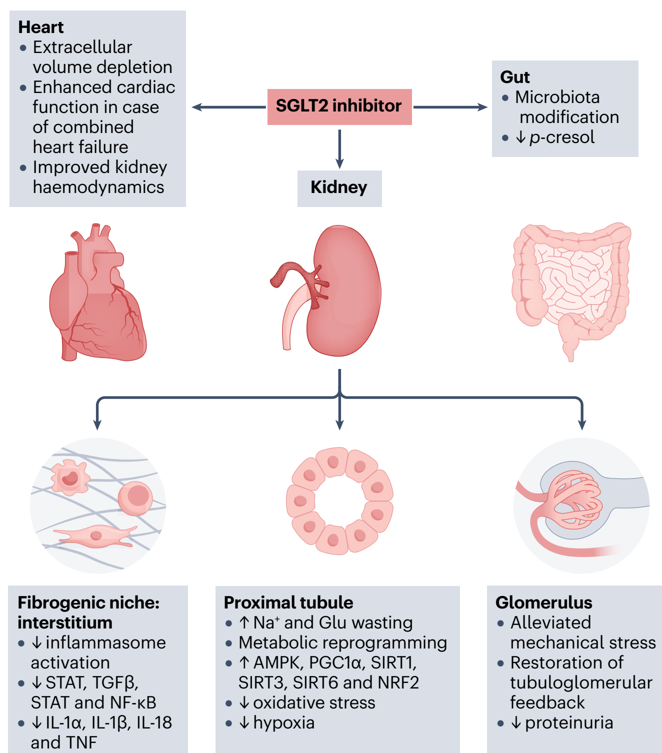

Fig. 4 | Effects of SGLT2 inhibitors on kidney compartments and mediators of fibrosis. Sodium–glucose co-transporter 2 (SGLT2) inhibitors can have an anti-fibrotic effect via diverse pathways. In the kidney, SGLT2 inhibitors mainly target the proximal tubule but they can also improve glomerular haemodynamics and inhibit the formation of a fibrogenic niche. Some of the nephroprotective effects of SGLT2 inhibitors can also be mediated by their interaction with the gut and its microbiota, as well as improved kidney vascularization owing to beneficial effects on the heart.

creatinine levels and decreased proteinuria, and prevented kidney fibrosis, thus mimicking the beneficial effects of a low-protein diet[140]. However, a Cochrane meta-analysis raised doubts about the feasibility and clinical relevance of this diet[141].

Metabolic acidosis was identified as an independent risk factor for CKD progression in large cohort studies[142]. According to a 2021 meta-analysis, correction of acidosis through exogenous sodium bicarbonate intake could delay the decline of kidney function and reduce the risk of progression to kidney failure[143]. The proposed mechanism is that metabolic acidosis increases ammoniagenesis in residual nephrons, which in turn leads to local complement activation and further damage in tubular cells. A link has also been proposed between metabolic acidosis and several factors decreasing kidney function such as ET-1, impaired cardiac function, chronic inflammation, muscle and bone catabolism and insulin resistance[143].

Future strategies

Refined patient selection

The development of a new generation of MRAs, SGLT2 inhibitors and ET-1 antagonists, provides clinicians with several new tools to slow the progression of CKD, although they might also prevent or delay the development of a new generation of anti-fibrotic drugs because of an important financial burden. The large phase III trials that demonstrated the efficiency of SGLT2 inhibitors and MRAs enrolled several thousand patients who were followed for 2–3 years to ensure adequate statistical power[123,135]. The development of any new anti-fibrotic agents will require evidence of superiority over existing nephroprotective drugs in long-term studies involving thousands of patients and therefore represents a high financial risk.

One cost-limiting solution involves lowering the threshold for eGFR reduction in the usual composite criterion for kidney failure progression. A 2023 study showed that opting for a 40% eGFR threshold instead of the standard 50% led to more frequent events, therefore lowering the number of patients required[133,144]. The same study proposed a new hierarchical composite end point that includes all-cause mortality, kidney failure, sustained 57%, 50% and 40% GFR decline from baseline, and GFR slope. A large dataset from seven major nephroprotective interventions compared with placebo was used to show that these criteria could drastically reduce the number of patients needed[145]. Nevertheless, these criteria primarily reflect late events in the progression of CKD and are driven by rapidly progressing disease, thus precluding the identification of early modulators of fibrosis. In 2023, the CKD-EPI Clinical Trials Consortium proposed eGFR slope as a sole surrogate end point to allow earlier evaluation and lower the cost of long follow-up periods[146]. However, a drop in eGFR can still be considered a late event given that it implies the destruction of at least 50% of the kidney parenchyma.

Progress in omics data generation and large data handling will allow the emergence of earlier endpoints. Identification of urinary and blood biomarkers that predict CKD progression risk is an active topic of kidney research[147]. One study proposed a urinary biomarker panel comprising 273 peptides (CKD 273) as a better evaluation tool than albuminuria in predicting fast progression in patients with normal eGFR[148]. These results were confirmed in the PRIORITY trial, which led to FDA approval[149].

Additional insights could be provided by the progress of non-invasive radiological methods for the detection of fibrosis. Several studies demonstrated that some MRI sequences are adapted to evaluate fibrosis and CKD progression risk in native and transplant kidneys[150,151]. Following a similar approach to detect liver fibrosis, several teams demonstrated that renal elastography is feasible, reproducible and correlates with histological evaluation of fibrosis[152,153]. A recent sonogram technique called ultrasound localization microscopy might also be useful. This technique allows the individual tracking of microbubbles injected into the bloodstream, improving the resolution of the microvascular bed up to tenfold; it even allows visualization of glomeruli in human native and transplanted kidneys[154,155]. Other investigators used collagen-binding fluorescent protein to assess kidney fibrosis in two models of acute kidney injury (UUO and ischaemia–reperfusion injury)[156]. This approach allows specific non-invasive quantification of perivascular and interstitial fibrosis and, with the improvement of fluorescent probes, can also be transferred to people with CKD. Several radiotracers and nanoplatforms are currently under development for the detection of fibrosis[157,158]. Alternative approaches have been explored using machine learning, particularly by applying recurrent neuronal network models to electronic health records. The aim of this method is to develop predictive models for early detection of patients who are at risk of progressing to late-stage CKD[159]. Large data-based algorithms can also be used to shorten clinical trial duration through early identification of patient trajectories[160].

Cell and metabolic reprogramming

Targeting metabolic dysregulation offers a promising avenue for fibrosis therapy. Metabolic shifts and adaptations have an important role in recovery and repair by supporting cell proliferation and redifferentiation[161,162]. However, following kidney injury, metabolic pathways are extensively reprogrammed, contributing to CKD progression[163]. Metabolite profiling has revealed a range of metabolic perturbations during pulmonary, hepatic and kidney fibrosis[164–167]. In CKD, impaired fatty acid oxidation pathways cause lipid accumulation and lipotoxicity, leading to cellular apoptosis, dedifferentiation, reduced ECM degradation and kidney fibrosis[168,169]. Reprogrammed glycolysis and mitochondrial metabolism contribute to disease progression in cirrhosis, kidney fibrosis and IPF[165,170,171].

The efficacy of therapies targeting metabolism has been demonstrated, for example, with drugs that target metabolism indirectly, such as the aforementioned SGLT2 inhibitors, pentoxifylline and GLP1RAs[138,172]. Preclinical studies have shown that inhibiting glycolysis is beneficial in UUO[171], skin fibrosis[173] and pulmonary fibrosis[170]. Similarly, an oxidative phosphorylation modulator attenuated mitochondrial metabolic fibrosis and inhibited pulmonary fibrosis[174].

The development of effective therapies targeting metabolic reprogramming must consider the diversity of the cells within fibrotic tissues, as they can have different metabolic profiles. Additionally, the central role and physiological functions of these pathways highlight the risk of side effects in other organs following systemic administration. Meanwhile, metabolome analysis of plasma and urine might facilitate precision medicine strategies, allowing the prediction of disease progression through the identification and monitoring of non-invasive biomarkers in early stages of CKD.

Nanotechnology and targeted drug delivery

Tissue-targeted drug delivery has emerged as a promising therapeutic innovation for the treatment of kidney fibrosis. Nanotechnology-based approaches offer targeted, controlled and less toxic alternatives to traditional methods by preserving healthy cells. These technologies use the encapsulation of various molecules including drugs, proteins and genetic material (including RNA and DNA, small interfering (siRNAs) and microRNAs). Viral vectors are the most widely used vehicles for drug delivery, but they can induce mutagenesis and immune responses in vivo, which has driven the investigation of non-viral vectors[175].

The small size of nanoparticles (1–100 nm) makes them attractive for drug delivery applications[176]. Nanoparticles can be engineered from various materials (synthetic or natural polymers, lipid and inorganic compounds) and modified with ligands or antibodies that specifically bind to surface molecules or receptors expressed on kidney cells[177]. Each category of nanoparticles offers distinct advantages and limitations. Lipid nanoparticles are renowned for their biocompatibility and biodegradability, yet there are potential risks of instability and opsonization leading to drug leakage and degradation[178]. Polymeric nanoparticles offer versatility and stability, but their chemical formulation can be cytotoxic and tissue penetration might be restricted[179]. For cancer therapy, conventional nanoparticles have been replaced by 'smart' nanoparticles that can be triggered by specific stimuli such as enzymes, pH and temperature, allowing them to efficiently aggregate at the target location and release their payloads[180,181].

An additional novel 'smart' strategy aimed at improving pharmaceutical formulation and drug delivery is the use of Janus particles[182]. These nano or micro-particles have two distinct compartments with different or opposite physicochemical properties, which allows the incorporation of a variety of drugs and enables them to cross different barriers (Fig. 5a). Janus particles can bear hydrophobic and hydrophilic groups in each half, and combine two different pharmaceutical agents in distinct compartments[183].

Extracellular vesicles (EVs) have also gained attention and grown in popularity as potential future therapeutic strategies. EVs, including apoptotic bodies (50–5,000 nm from apoptosis fragmentation), exosomes (30–100 nm from internal budding of the endosomal membrane) and macrovesicles (100–1,000 nm from the budding plasma membrane) are naturally released from almost all cells and are found in body fluids (for example, urine, blood and breast milk)[184,185]. EVs are involved in physiological and pathological processes, including tissue regeneration and repair, immune response modulation, and cell–cell communication[186,187]. The composition of the EV membrane is similar to that of the cell membrane, which confers the advantage of low immunogenicity, biocompatibility and ability to cross biological barriers[185,188]. Evidence from preclinical models in CKD showed the benefits of EVs derived from mesenchymal stromal cells (MSCs) in kidney recovery by decreasing the expression of inflammatory cytokines (IL-6, TNF and IL-1β) and mitigating tubular fibrosis in the UUO model, and by down-regulating pro-fibrotic genes in aristolochic acid-induced CKD[189,190]. Injections of BM-MSC EVs prevented kidney failure in the UUO model[191]. Additionally, the delivery of antifibrotic microRNAs via BM-MSC EVs in a mouse model of streptozotocin-induced diabetic nephropathy reversed kidney fibrosis[192].

The use of EVs in patients is currently limited. Their safety and efficacy has been reported in some clinical trials, only one of which involved people with CKD, where the therapy significantly improved eGFR, serum creatinine levels and blood urea[193]. The main reason for this limited use of EVs is their heterogeneous and diverse nature, as well as inconsistent isolation and purification procedures. The use of synthetic extracellular vesicles mimicking endogenous EVs is a promising alternative that might overcome these limitations (Fig. 5b).

Conclusions

Although CKD is defined by a decline in GFR, ECM accumulation is a hallmark of the disease leading to structural deterioration and irreversible loss of kidney function. Over the past decades, research has provided remarkable insights into the cellular and molecular mechanisms of pathological fibrogenesis, and several key elements of the fibrotic process have been identified. Fibrosis and the creation of the fibrotic niche are now firmly established as dynamic processes that involve a complex interplay of different signalling pathways, from cytokines and inflammatory molecules to growth factors and vasoconstrictors. Among them, the TGFβ superfamily has emerged as a key component of the fibrotic process and several approaches have been developed to block TGFβ signalling.

Nevertheless, the complex interactions that create and maintain the kidney fibrotic niche have complicated therapeutic development and most clinical trials of TGFβ-targeting drugs have been discontinued owing to substantial side effects. This setback was counterbalanced by the addition of improved generations of MRAs and ET_A blockers to the antihypertensive arsenal, and by the emergence of SGLT2 inhibitors, which provided unexpected therapeutic benefits. The rapid development of nanotechnologies, imaging techniques and bioinformatics create additional opportunities for precision medicine. To maximize their potential, new therapeutic approaches must be integrated with a

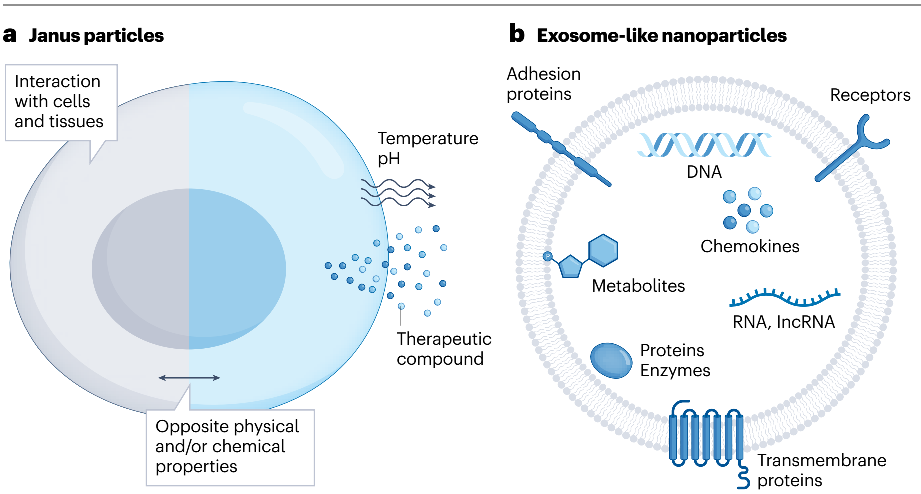

Fig. 5 | Janus particles and exosome-like nanoparticles. a, Janus particles have two distinct compartments with different and opposing physicochemical properties. For example, each part can carry hydrophobic or hydrophilic compounds and combine two different pharmaceutical actions. **b**, Exosome-like nanoparticles enable the delivery of drugs to tissues in a controlled and targeted manner through the encapsulation of various molecules, including pharmaceutical drugs, proteins and/or genetic material such as RNA and DNA.

deep understanding of underlying disease mechanisms. Importantly, clinical research must also consider the complexity of fibrogenic signalling, the diversity of the cell types involved and the differences in organs and diseases to realize the goal of developing an effective anti-fibrotic therapy in CKD.

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References

1. Ong, K. L. et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* **402**, 203–234 (2023).
2. Sundström, J. et al. Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2·4 million patients from 11 countries: the CaReMe CKD study. *Lancet Reg. Health Eur.* **20**, 100438 (2022).
3. Boffa, J. J. et al. Angiotensin II activates collagen type I gene in the renal vasculature of transgenic mice during inhibition of nitric oxide synthesis: evidence for an endothelin-mediated mechanism. *Circulation* **100**, 1901–1908 (1999).
4. Cho, J. J. et al. An oral endothelin-A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis. *Gastroenterology* **118**, 1169–1178 (2000).
5. Li, L., Fu, H. & Liu, Y. The fibrogenic niche in kidney fibrosis: components and mechanisms. *Nat. Rev. Nephrol.* **18**, 545–557 (2022).
6. Klingberg, F., Hinz, B. & White, E. S. The myofibroblast matrix: implications for tissue repair and fibrosis. *J. Pathol.* **229**, 298–309 (2013).
7. Tanaka, S., Portilla, D. & Okusa, M. D. Role of perivascular cells in kidney homeostasis, inflammation, repair and fibrosis. *Nat. Rev. Nephrol.* **19**, 721–732 (2023).
8. Huang, R., Fu, P. & Ma, L. Kidney fibrosis: from mechanisms to therapeutic medicines. *Signal. Transduct. Target. Ther.* **8**, 1–20 (2023).
9. Kuppe, C. et al. Decoding myofibroblast origins in human kidney fibrosis. *Nature* **589**, 281–286 (2021).
10. Cohen, C. et al. WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease. *Nat. Commun.* **15**, 743 (2024).
11. Wu, L. et al. Peritubular capillary dysfunction and renal tubular epithelial cell stress following lipopolysaccharide administration in mice. *Am. J. Physiol. Renal Physiol.* **292**, F261–F268 (2007).
12. Schrimpf, C., Teebken, O. E., Wilhelmi, M. & Duffield, J. S. The role of pericyte detachment in vascular rarefaction. *J. Vasc. Res.* **51**, 247–258 (2014).
13. Ferenbach, D. A. & Bonventre, J. V. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. *Nat. Rev. Nephrol.* **11**, 264–276 (2015).
14. Moretti, L., Stalfort, J., Barker, T. H. & Abebayehu, D. The interplay of fibroblasts, the extracellular matrix, and inflammation in scar formation. *J. Biol. Chem.* **298**, 101530 (2022).
15. Tecklenborg, J., Clayton, D., Siebert, S. & Coley, S. M. The role of the immune system in kidney disease. *Clin. Exp. Immunol.* **192**, 142 (2018).
16. Roumeliotis, S., Mallamaci, F. & Zoccali, C. Endothelial dysfunction in chronic kidney disease, from biology to clinical outcomes: a 2020 update. *J. Clin. Med.* **9**, 2359 (2020).
17. Cao, Q., Harris, D. C. H. & Wang, Y. Macrophages in kidney injury, inflammation, and fibrosis. *Physiol. Bethesda Md.* **30**, 183–194 (2015).
18. Henderson, N. C. et al. Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. *Am. J. Pathol.* **172**, 288–298 (2008).
19. Ryu, S. et al. Siglec-F-expressing neutrophils are essential for creating a profibrotic microenvironment in renal fibrosis. *J. Clin. Invest.* **132**, e156876 (2022).
20. Shen, B., Liu, X., Fan, Y. & Qiu, J. Macrophages regulate renal fibrosis through modulating TGFβ superfamily signaling. *Inflammation* **37**, 2076–2084 (2014).
21. Pardo, A. et al. Increase of lung neutrophils in hypersensitivity pneumonitis is associated with lung fibrosis. *Am. J. Respir. Crit. Care Med.* **161**, 1698–1704 (2000).
22. Duffield, J. S. et al. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. *J. Clin. Invest.* **115**, 56–65 (2005).
23. Gebru, Y. A. et al. T cell subsets and natural killer cells in the pathogenesis of nonalcoholic fatty liver disease. *Int. J. Mol. Sci.* **22**, 12190 (2021).
24. Burfeind, K. G., Funahashi, Y., Munhall, A. C., Eiwaz, M. & Hutchens, M. P. Natural killer lymphocytes mediate renal fibrosis due to acute cardiorenal syndrome. *Kidney360* **5**, 8–21 (2024).
25. Bonner, J. C. Regulation of PDGF and its receptors in fibrotic diseases. *Cytokine Growth Factor Rev.* **15**, 255–273 (2004).
26. Biernacka, A., Dobaczewski, M. & Frangogiannis, N. G. TGF-β signaling in fibrosis. *Growth Factors* **29**, 196–202 (2011).
27. Beljaars, L., Daliri, S., Dijkhuizen, C., Poelstra, K. & Gosens, R. WNT-5A regulates TGF-β-related activities in liver fibrosis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **312**, G219–G227 (2017).
28. Liu, J., Wang, F. & Luo, F. The role of JAK/STAT pathway in fibrotic diseases: molecular and cellular mechanisms. *Biomolecules* **13**, 119 (2023).
29. Contreras, O. et al. Cross-talk between TGF-β and PDGFRα signaling pathways regulates the fate of stromal fibro-adipogenic progenitors. *J. Cell Sci.* **132**, jcs232157 (2019).
30. Sun, Y., Zhang, Y. & Chi, P. Pirfenidone suppresses TGF-β1-induced human intestinal fibroblasts activities by regulating proliferation and apoptosis via the inhibition of the Smad and PI3K/AKT signaling pathway. *Mol. Med. Rep.* **18**, 3907–3913 (2018).
31. Morimoto, Y. et al. TNF-α deficiency accelerates renal tubular interstitial fibrosis in the late stage of ureteral obstruction. *Exp. Mol. Pathol.* **85**, 207–213 (2008).
32. Widjaja, A. A. et al. Targeting endogenous kidney regeneration using anti-IL11 therapy in acute and chronic models of kidney disease. *Nat. Commun.* **13**, 7497 (2022).
33. Wight, T. N. & Potter-Perigo, S. The extracellular matrix: an active or passive player in fibrosis? *Am. J. Physiol. Gastrointest. Liver Physiol.* **301**, G950–G955 (2011).
34. AlQudah, M., Hale, T. M. & Czubryt, M. P. Targeting the renin-angiotensin-aldosterone system in fibrosis. *Matrix Biol. J. Int. Soc. Matrix Biol.* **91–92**, 92–108 (2020).
35. Zhao, Y., Sun, Z., Li, L., Yuan, W. & Wang, Z. Role of collagen in vascular calcification. *J. Cardiovasc. Pharmacol.* **80**, 769–778 (2022).
36. Saunders, J. T. & Schwarzbauer, J. E. Fibronectin matrix as a scaffold for procollagen proteinase binding and collagen processing. *Mol. Biol. Cell* **30**, 2218–2226 (2019).
37. Bülow, R. D. & Boor, P. Extracellular matrix in kidney fibrosis: more than just a scaffold. *J. Histochem. Cytochem.* **67**, 643–661 (2019).
38. Tan, R. J. & Liu, Y. Matrix metalloproteinases in kidney homeostasis and diseases. *Am. J. Physiol. Renal Physiol.* **302**, F1351–F1361 (2012).
39. Shweke, N. et al. Tissue transglutaminase contributes to interstitial renal fibrosis by favoring accumulation of fibrillar collagen through TGF-β activation and cell infiltration. *Am. J. Pathol.* **173**, 631–642 (2008).
40. Swigris, J. J. & Brown, K. K. The role of endothelin-1 in the pathogenesis of idiopathic pulmonary fibrosis. *BioDrugs* **24**, 49–54 (2010).
41. Kohan, D. E. & Barton, M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int.* **86**, 896–904 (2014).
42. Roberts, A. B. et al. Transforming growth factor type beta: rapid induction of fibrosis and angiogenesis in vivo and stimulation of collagen formation in vitro. *Proc. Natl Acad. Sci. USA* **83**, 4167–4171 (1986).
43. Deng, Z. et al. TGF-β signaling in health, disease and therapeutics. *Signal. Transduct. Target. Ther.* **9**, 1–40 (2024).
44. Mogyorosi, A. What is the role of decorin in diabetic kidney disease? *Nephrol. Dial. Transplant.* **14**, 1078–1081 (1999).
45. Klahr, S. The bone morphogenetic proteins (BMPs). Their role in renal fibrosis and renal function. *J. Nephrol.* **16**, 179–185 (2003).
46. Trachtman, H. et al. A phase 1, single-dose study of fresolimumab, an anti-TGF-β antibody, in treatment-resistant primary focal segmental glomerulosclerosis. *Kidney Int.* **79**, 1236–1243 (2011).
47. Vincenti, F. et al. A phase 2, double-blind, placebo-controlled, randomized study of fresolimumab in patients with steroid-resistant primary focal segmental glomerulosclerosis. *Kidney Int. Rep.* **2**, 800–810 (2017).
48. Morris, J. C. et al. Phase I study of GC1008 (fresolimumab): a human anti-transforming growth factor-beta (TGFβ) monoclonal antibody in patients with advanced malignant melanoma or renal cell carcinoma. *PLoS ONE* **9**, e90353 (2014).
49. Pergola, P. E. et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N. Engl. J. Med.* **365**, 327–336 (2011).
50. Nangaku, M. et al. Randomized clinical trial on the effect of bardoxolone methyl on GFR in diabetic kidney disease patients (TSUBAKI Study). *Kidney Int. Rep.* **5**, 879–890 (2020).
51. Chin, M. P. et al. Risk factors for heart failure in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease treated with bardoxolone methyl. *J. Card. Fail.* **20**, 953–958 (2014).
52. Rossing, P. et al. Effect of bardoxolone methyl on the urine albumin-to-creatinine ratio in patients with type 2 diabetes and stage 4 chronic kidney disease. *Kidney Int.* **96**, 1030–1036 (2019).
53. Baker, M. A. et al. Tissue-specific MicroRNA expression patterns in four types of kidney disease. *J. Am. Soc. Nephrol.* **28**, 2985 (2017).
54. Zang, J., Maxwell, A. P., Simpson, D. A. & McKay, G. J. Differential expression of urinary exosomal microRNAs miR-21-5p and miR-30b-5p in individuals with diabetic kidney disease. *Sci. Rep.* **9**, 10900 (2019).
55. Annes, J. P., Chen, Y., Munger, J. S. & Rifkin, D. B. Integrin αVβ6-mediated activation of latent TGF-β requires the latent TGF-β binding protein-1. *J. Cell Biol.* **165**, 723–734 (2004).
56. Raghu, G. et al. Randomized phase IIa clinical study of an anti-αvβ6 monoclonal antibody in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* **206**, 1166–1168 (2022).
57. Lo, D. J. et al. Inhibition of αvβ6 promotes acute renal allograft rejection in nonhuman primates. *Am. J. Transplant.* **13**, 3085–3093 (2013).
58. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT00878761 (2011).
59. Choi, K. et al. Pirfenidone inhibits transforming growth factor-β1-induced fibrogenesis by blocking nuclear translocation of Smads in human retinal pigment epithelial cell line ARPE-19. *Mol. Vis.* **18**, 1010–1020 (2012).
60. Burghardt, I. et al. Pirfenidone inhibits TGF-β expression in malignant glioma cells. *Biochem. Biophys. Res. Commun.* **354**, 542–547 (2007).
61. Park, H.-S. et al. Pirfenidone suppressed the development of glomerulosclerosis in the FGS/Kist mouse. *J. Korean Med. Sci.* **18**, 527–533 (2003).
62. King, T. E. et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **370**, 2083–2092 (2014).
63. Cho, M. E., Smith, D. C., Branton, M. H., Penzak, S. R. & Kopp, J. B. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. *Clin. J. Am. Soc. Nephrol.* **2**, 906 (2007).

64. Sharma, K. et al. Pirfenidone for diabetic nephropathy. *J. Am. Soc. Nephrol.* **22**, 1144–1151 (2011).
65. Lancaster, L. H. et al. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. *Eur. Respir. Rev.* **26**, 170057 (2017).
66. Xu, X. et al. Hydronidone ameliorates liver fibrosis by inhibiting activation of hepatic stellate cells via Smad7-mediated degradation of TGFβRI. *Liver Int.* **43**, 2523–2537 (2023).
67. Cai, X. et al. Hydronidone for the treatment of liver fibrosis related to chronic hepatitis B: a phase 2 randomized controlled trial. *Clin. Gastroenterol. Hepatol.* **21**, 1893–1901.e7 (2023).
68. Lin, Y., Xu, Z., Zhou, B., Ma, K. & Jiang, M. Pentoxifylline inhibits pulmonary fibrosis by regulating cellular senescence in mice. *Front. Pharmacol.* **13**, 848263 (2022).
69. Demircan, V. et al. Evaluation of therapeutic use of a combination of pentoxifylline and vitamin E in radiation-induced renal fibrosis. *Sci. Rep.* **14**, 6977 (2024).
70. Navarro-González, J. F. et al. Effects of pentoxifylline on soluble klotho concentrations and renal tubular cell expression in diabetic kidney disease. *Diabetes Care* **41**, 1817–1820 (2018).
71. Moosaie, F. et al. Effects of pentoxifylline on serum markers of diabetic nephropathy in type 2 diabetes. *Diabetes Ther.* **13**, 1023–1036 (2022).
72. Liu, F. et al. Nintedanib, a triple tyrosine kinase inhibitor, attenuates renal fibrosis in chronic kidney disease. *Clin. Sci. Lond. Engl.* **131**, 2125–2143 (2017).
73. Feng, L. et al. Synergistic inhibition of renal fibrosis by nintedanib and gefitinib in a murine model of obstructive nephropathy. *Kidney Dis.* **7**, 34–49 (2021).
74. Jamadar, A. et al. The tyrosine-kinase inhibitor nintedanib ameliorates autosomal-dominant polycystic kidney disease. *Cell Death Dis.* **12**, 947 (2021).
75. Saint-Pierre, M. Tolerability of nintedanib in severe chronic kidney disease (CKD): a case study. *Chest* **156**, A1309 (2019).
76. Hasegawa, M. et al. Nintedanib-induced glomerular microangiopathy: a case report. *Cen. Case Rep.* **9**, 295–300 (2020).
77. Inoue, D. et al. Renal thrombotic microangiopathy during nintedanib treatment for idiopathic pulmonary fibrosis. *Clin. Nephrol.* **93**, 47–50 (2020).
78. Brosius, F. C. & He, J. C. JAK inhibition and progressive kidney disease. *Curr. Opin. Nephrol. Hypertens.* **24**, 88–95 (2015).
79. Mascarenhas, J. & Hoffman, R. Ruxolitinib: the first FDA approved therapy for the treatment of myelofibrosis. *Clin. Cancer Res.* **18**, 3008–3014 (2012).
80. Saha, C. & Harrison, C. Fedratinib, the first selective JAK2 inhibitor approved for treatment of myelofibrosis — an option beyond ruxolitinib. *Expert. Rev. Hematol.* **15**, 583–595 (2022).
81. Wallace, D. J. et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* **392**, 222–231 (2018).
82. Petri, M. et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *Lancet* **401**, 1011–1019 (2023).
83. Tuttle, K. R. et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a phase 2 randomized controlled clinical trial. *Nephrol. Dial. Transplant.* **33**, 1950–1959 (2018).
84. Sattar, N. et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* **9**, 653–662 (2021).
85. Schechter, M. et al. Kidney function loss and albuminuria progression with GLP-1 receptor agonists versus basal insulin in patients with type 2 diabetes: real-world evidence. *Cardiovasc. Diabetol.* **22**, 126 (2023).
86. Perkovic, V. et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N. Engl. J. Med.* **391**, 109–121 (2024).
87. Alicic, R. Z., Cox, E. J., Neumiller, J. J. & Tuttle, K. R. Incretin drugs in diabetic kidney disease: biological mechanisms and clinical evidence. *Nat. Rev. Nephrol.* **17**, 227–244 (2021).
88. Simms-Williams, N. et al. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study. *BMJ* **385**, e078242 (2024).
89. Kalyanaraman, H. et al. Nongenomic thyroid hormone signaling occurs through a plasma membrane-localized receptor. *Sci. Signal.* **7**, ra48–ra48 (2014).
90. Alonso-Merino, E. et al. Thyroid hormones inhibit TGF-β signaling and attenuate fibrotic responses. *Proc. Natl Acad. Sci. USA* **113**, E3451–E3460 (2016).
91. Harrison, S. A. et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N. Engl. J. Med.* **390**, 497–509 (2024).
92. He, S., Yao, L. & Li, J. Role of MCP-1/CCR2 axis in renal fibrosis: mechanisms and therapeutic targeting. *Medicine* **102**, e35613 (2023).
93. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT05183646 (2023).
94. Donati, C., Cencetti, F., Bernacchioni, C., Vannuzzi, V. & Bruni, P. Role of sphingosine 1-phosphate signalling in tissue fibrosis. *Cell. Signal.* **78**, 109861 (2021).
95. Sasaki, S., Bao, Q. & Hughes, R. C. Galectin-3 modulates rat mesangial cell proliferation and matrix synthesis during experimental glomerulonephritis induced by anti-Thy1.1 antibodies. *J. Pathol.* **187**, 481–489 (1999).
96. Ou, S.-M. et al. Urinary galectin-3 as a novel biomarker for the prediction of renal fibrosis and kidney disease progression. *Biomedicines* **10**, 585 (2022).
97. Frenay, A.-R. S. et al. Pharmacological inhibition of galectin-3 protects against hypertensive nephropathy. *Am. J. Physiol. Renal Physiol.* **308**, F500–F509 (2015).
98. Chien, J.-W. et al. Daily urinary interleukin-11 excretion correlated with proteinuria in IgA nephropathy and lupus nephritis. *Pediatr. Nephrol.* **21**, 490–496 (2006).
99. Bigaeva, E. et al. Transcriptomic characterization of culture-associated changes in murine and human precision-cut tissue slices. *Arch. Toxicol.* **93**, 3549–3583 (2019).
100. Cook, S. A. & Schafer, S. Hiding in plain sight: interleukin-11 emerges as a master regulator of fibrosis, tissue integrity, and stromal inflammation. *Annu. Rev. Med.* **71**, 263–276 (2020).
101. Li, Y. et al. Renal fibrosis is alleviated through targeted inhibition of IL-11-induced renal tubular epithelial-to-mesenchymal transition. *Am. J. Pathol.* **193**, 1936–1952 (2023).
102. Widjaja, A. A. et al. A neutralizing IL-11 antibody improves renal function and increases lifespan in a mouse model of Alport syndrome. *J. Am. Soc. Nephrol.* **33**, 718 (2022).
103. Tang, X. et al. Assessment of Brd4 inhibition in idiopathic pulmonary fibrosis lung fibroblasts and *in vivo* models of lung fibrosis. *Am. J. Pathol.* **183**, 470–479 (2013).
104. Kulikowski, E. et al. Apabetalone mediated epigenetic modulation is associated with favorable kidney function and alkaline phosphatase profile in patients with chronic kidney disease. *Kidney Blood Press. Res.* **43**, 449–457 (2018).
105. Kalantar-Zadeh, K. et al. Effect of apabetalone on cardiovascular events in diabetes, CKD, and recent acute coronary syndrome: results from the BETonMACE randomized controlled trial. *Clin. J. Am. Soc. Nephrol.* **16**, 705 (2021).
106. US National Library of Medicine. *Clinicaltrials.gov* https://clinicaltrials.gov/study/NCT03228940 (2023).
107. Cheung, A. K. et al. Effects of intensive BP control in CKD. *J. Am. Soc. Nephrol.* **28**, 2812–2823 (2017).
108. Zhang, Y. et al. ACE inhibitor benefit to kidney and cardiovascular outcomes for patients with non-dialysis chronic kidney disease stages 3–5: a network meta-analysis of randomised clinical trials. *Drugs* **80**, 797–811 (2020).
109. Xie, X. et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a Bayesian network meta-analysis of randomized clinical trials. *Am. J. Kidney Dis.* **67**, 728–741 (2016).
110. Agarwal, R. et al. Chlorthalidone for hypertension in advanced chronic kidney disease. *N. Engl. J. Med.* **385**, 2507–2519 (2021).
111. Bhandari, S. et al. Evaluation of the stopping angiotensin converting enzyme inhibitor compared to angiotensin receptor blocker (STOP ACEi trial) in advanced and progressive chronic kidney disease. *Kidney Int.* **105**, 200–208 (2024).
112. Nakayama, T. et al. Effects of renin-angiotensin system inhibitors on the incidence of unplanned dialysis. *Hypertens. Res.* **45**, 1018–1027 (2022).
113. Ruiz-Ortega, M., Rayego-Mateos, S., Lamas, S., Ortiz, A. & Rodrigues-Diez, R. R. Targeting the progression of chronic kidney disease. *Nat. Rev. Nephrol.* **16**, 269–288 (2020).
114. Desai, A. S. et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N. Engl. J. Med.* **389**, 228–238 (2023).
115. Bakris, G. L. et al. RNA interference with zilebesiran for mild to moderate hypertension: the KARDIA-1 randomized clinical trial. *JAMA* **331**, 740–749 (2024).
116. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT05103332 (2024).
117. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT06272487 (2025).
118. Epstein, M., Kovesdy, C. P., Clase, C. M., Sood, M. M. & Pecoits-Filho, R. Aldosterone, mineralocorticoid receptor activation, and CKD: a review of evolving treatment paradigms. *Am. J. Kidney Dis.* **80**, 658–666 (2022).
119. Rossing, K., Schjoedt, K. J., Smidt, U. M., Boomsma, F. & Parving, H.-H. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. *Diabetes Care* **28**, 2106–2112 (2005).
120. Epstein, M. et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin. J. Am. Soc. Nephrol.* **1**, 940 (2006).
121. Agarwal, R. et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur. Heart J.* **43**, 474–484 (2022).
122. Stevens, P. E. et al. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* **105**, S117–S314 (2024).
123. Zhu, Z. et al. Finerenone added to RAS/SGLT2 blockade for CKD in Alport syndrome. Results of a randomized controlled trial with *Col4a3−/−* mice. *J. Am. Soc. Nephrol.* **34**, 1513–1520 (2023).
124. Freeman, M. W. et al. Phase 2 trial of baxdrostat for treatment-resistant hypertension. *N. Engl. J. Med.* **388**, 395–405 (2023).
125. Guan, Z., VanBeusecum, J. P. & Inscho, E. W. Endothelin and the renal vasculature. *Semin. Nephrol.* **35**, 145–155 (2015).
126. Benigni, A., Buelli, S. & Kohan, D. E. Endothelin-targeted new treatments for proteinuric and inflammatory glomerular diseases: focus on the added value to anti-renin-angiotensin system inhibition. *Pediatr. Nephrol.* **36**, 763–775 (2021).
127. Wei, A. et al. Clinical adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. *J. Am. Heart Assoc.* **5**, e003896 (2016).
128. Heerspink, H. J. L. et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet* **393**, 1937–1947 (2019).
129. Rovin, B. H. et al. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. *Lancet* **402**, 2077–2090 (2023).

130. Rheault, M. N. et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis. *N. Engl. J. Med.* **389**, 2436–2445 (2023).
131. Heerspink, H. J. L. et al. Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial. *Lancet* **402**, 2004–2017 (2023).
132. Perkovic, V. et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N. Engl. J. Med.* **380**, 2295–2306 (2019).
133. Heerspink, H. J. L. et al. Dapagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **383**, 1436–1446 (2020).
134. Empagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **388**, 117–127 (2023).
135. Heerspink, H. J. L., Perkins, B. A., Fitchett, D. H., Husain, M. & Cherney, D. Z. I. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* **134**, 752–772 (2016).
136. Castoldi, G. et al. Sodium glucose cotransporter-2 inhibitors in non-diabetic kidney disease: evidence in experimental models. *Pharmaceuticals* **17**, 362 (2024).
137. Chen, X., Hocher, C.-F., Shen, L., Krämer, B. K. & Hocher, B. Reno- and cardioprotective molecular mechanisms of SGLT2 inhibitors beyond glycemic control: from bedside to bench. *Am. J. Physiol. Cell Physiol.* **325**, C661–C681 (2023).
138. Billing, A. M. et al. Metabolic communication by SGLT2 inhibition. *Circulation* **149**, 860–884 (2024).
139. Kalantar-Zadeh, K. & Fouque, D. Nutritional management of chronic kidney disease. *N. Engl. J. Med.* **377**, 1765–1776 (2017).
140. Barba, C. et al. A low aromatic amino-acid diet improves renal function and prevent kidney fibrosis in mice with chronic kidney disease. *Sci. Rep.* **11**, 19184 (2021).
141. Hahn, D., Hodson, E. M. & Fouque, D. Low protein diets for non-diabetic adults with chronic kidney disease. *Cochrane Database Syst. Rev.* **10**, CD001892 (2020).
142. Anderson, A. H. et al. Novel risk factors for progression of diabetic and nondiabetic CKD: findings from the chronic renal insufficiency cohort (CRIC) study. *Am. J. Kidney Dis.* **77**, 56–73.e1 (2021).
143. Hultin, S. et al. A systematic review and meta-analysis on effects of bicarbonate therapy on kidney outcomes. *Kidney Int. Rep.* **6**, 695–705 (2021).
144. Heerspink, H. J. L. et al. Effects of newer kidney protective agents on kidney endpoints provide implications for future clinical trials. *Kidney Int.* **104**, 181–188 (2023).
145. Heerspink, H. L. et al. Development and validation of a new hierarchical composite end point for clinical trials of kidney disease progression. *J. Am. Soc. Nephrol.* **34**, 2025–2038 (2023).
146. Inker, L. A. et al. A meta-analysis of GFR slope as a surrogate endpoint for kidney failure. *Nat. Med.* **29**, 1867–1876 (2023).
147. Rupprecht, H. et al. Assessment and risk prediction of chronic kidney disease and kidney fibrosis using non-invasive biomarkers. *Int. J. Mol. Sci.* **25**, 3678 (2024).
148. Pontillo, C. et al. A urinary proteome-based classifier for the early detection of decline in glomerular filtration. *Nephrol. Dial. Transplant.* **32**, 1510–1516 (2017).
149. Tofte, N. et al. Early detection of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomised placebo-controlled trial. *Lancet Diabetes Endocrinol.* **8**, 301–312 (2020).
150. Berchtold, L. et al. Diffusion-magnetic resonance imaging predicts decline of kidney function in chronic kidney disease and in patients with a kidney allograft. *Kidney Int.* **101**, 804–813 (2022).
151. Zhao, D. et al. Amide proton transfer-weighted magnetic resonance imaging for application in renal fibrosis: a radiological-pathological based analysis. *Am. J. Nephrol.* **55**, 334–344 (2024).
152. Chen, Z. et al. Association of renal elasticity evaluated by real-time shear wave elastography with renal fibrosis in patients with chronic kidney disease. *Br. J. Radiol.* **97**, 392–398 (2024).
153. Mancianti, N. et al. Using renal elastography to predict the therapeutic response of nephrological patients. *J. Clin. Med.* **12**, 7385 (2023).
154. Bodard, S. et al. Visualization of renal glomeruli in human native kidneys with sensing ultrasound localization microscopy. *Invest. Radiol.* **59**, 561–568 (2024).
155. Bodard, S. et al. Ultrasound localization microscopy of the human kidney allograft on a clinical ultrasound scanner. *Kidney Int.* **103**, 930–935 (2023).
156. Baues, M. et al. Collagen-specific molecular imaging of renal fibrosis. *Kidney Int.* **97**, 609–614 (2020).
157. Izquierdo-Garcia, D. et al. Biodistribution, dosimetry, and pharmacokinetics of 68Ga-CBP8: a type I collagen-targeted PET probe. *J. Nucl. Med. Publ. Soc. Nucl. Med.* **64**, 775–781 (2023).
158. Ji, C. et al. Engineered extracellular vesicle-encapsulated CHIP as novel nanotherapeutics for treatment of renal fibrosis. *NPJ Regen. Med.* **9**, 1–11 (2024).
159. Zhu, Y., Bi, D., Saunders, M. & Ji, Y. Prediction of chronic kidney disease progression using recurrent neural network and electronic health records. *Sci. Rep.* **13**, 22091 (2023).
160. Aubert, O. et al. Application of the iBox prognostication system as a surrogate endpoint in the TRANSFORM randomised controlled trial: proof-of-concept study. *BMJ Open.* **11**, e052138 (2021).
161. Crotta, S. et al. Repair of airway epithelia requires metabolic rewiring towards fatty acid oxidation. *Nat. Commun.* **14**, 721 (2023).
162. Wang, Z. et al. Metabolic reprogramming in skin wound healing. *Burn. Trauma.* **12**, tkad047 (2024).
163. Li, Y., Sha, Z. & Peng, H. Metabolic reprogramming in kidney diseases: evidence and therapeutic opportunities. *Int. J. Nephrol.* **2021**, 5497346 (2021).
164. Tokushige, K. et al. Serum metabolomic profile and potential biomarkers for severity of fibrosis in nonalcoholic fatty liver disease. *J. Gastroenterol.* **48**, 1392–1400 (2013).
165. Zhao, Y.-Y. Metabolomics in chronic kidney disease. *Clin. Chim. Acta* **422**, 59–69 (2013).
166. Kang, Y. P. et al. Metabolic profiling regarding pathogenesis of idiopathic pulmonary fibrosis. *J. Proteome Res.* **15**, 1717–1724 (2016).
167. Miguel, V., Shaw, I. W. & Kramann, R. Metabolism at the crossroads of inflammation and fibrosis in chronic kidney disease. *Nat. Rev. Nephrol.* **21**, 39–56 (2024).
168. Afshinnia, F. et al. Impaired β-oxidation and altered complex lipid fatty acid partitioning with advancing CKD. *J. Am. Soc. Nephrol.* **29**, 295 (2018).
169. Mitrofanova, A., Merscher, S. & Fornoni, A. Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease. *Nat. Rev. Nephrol.* **19**, 629–645 (2023).
170. Xie, N. et al. Glycolytic reprogramming in myofibroblast differentiation and lung fibrosis. *Am. J. Respir. Crit. Care Med.* **192**, 1462–1474 (2015).
171. Ding, H. et al. Inhibiting aerobic glycolysis suppresses renal interstitial fibroblast activation and renal fibrosis. *Am. J. Physiol. Renal Physiol.* **313**, F561–F575 (2017).
172. Wester, A., Shang, Y., Toresson Grip, E., Matthews, A. A. & Hagström, H. Glucagon-like peptide-1 receptor agonists and risk of major adverse liver outcomes in patients with chronic liver disease and type 2 diabetes. *Gut* **73**, 835–843 (2024).
173. Zhao, X. et al. Metabolic regulation of dermal fibroblasts contributes to skin extracellular matrix homeostasis and fibrosis. *Nat. Metab.* **1**, 147–157 (2019).
174. Willette, R. N. et al. Modulation of oxidative phosphorylation with IM156 attenuates mitochondrial metabolic reprogramming and inhibits pulmonary fibrosis. *J. Pharmacol. Exp. Ther.* **379**, 290–300 (2021).
175. Dogbey, D. M. et al. Technological advances in the use of viral and non-viral vectors for delivering genetic and non-genetic cargos for cancer therapy. *Drug. Deliv. Transl. Res.* **13**, 2719–2738 (2023).
176. Khan, I., Saeed, K. & Khan, I. Nanoparticles: properties, applications and toxicities. *Arab. J. Chem.* **12**, 908–931 (2019).
177. Joudeh, N. & Linke, D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *J. Nanobiotechnol.* **20**, 262 (2022).
178. Moghimi, S. M. & Simberg, D. Complement activation turnover on surfaces of nanoparticles. *Nano Today* **15**, 8–10 (2017).
179. Suriya Prabha, A. et al. in *Nanotoxicity* (eds Rajendran, S. et al.) Ch. 7, 143–165 (Elsevier, 2020).
180. Lee, B. K., Yun, Y. H. & Park, K. Smart nanoparticles for drug delivery: boundaries and opportunities. *Chem. Eng. Sci.* **125**, 158–164 (2015).
181. Sun, L. et al. Smart nanoparticles for cancer therapy. *Signal. Transduct. Target. Ther.* **8**, 1–28 (2023).
182. Perro, A., Reculusa, S., Ravaine, S., Bourgeat-Lami, E. & Duguet, E. Design and synthesis of Janus micro- and nanoparticles. *J. Mater. Chem.* **15**, 3745–3760 (2005).
183. Walther, A. & Müller, A. H. E. Janus particles: synthesis, self-assembly, physical properties, and applications. *Chem. Rev.* **113**, 5194–5261 (2013).
184. Torregrosa Paredes, P. et al. Differences in exosome populations in human breast milk in relation to allergic sensitization and lifestyle. *Allergy* **69**, 463–471 (2014).
185. Zaborowski, M. P., Balaj, L., Breakefield, X. O. & Lai, C. P. Extracellular vesicles: composition, biological relevance, and methods of study. *Bioscience* **65**, 783–797 (2015).
186. Robbins, P. D. & Morelli, A. E. Regulation of immune responses by extracellular vesicles. *Nat. Rev. Immunol.* **14**, 195–208 (2014).
187. Nagelkerke, A. et al. Extracellular vesicles for tissue repair and regeneration: evidence, challenges and opportunities. *Adv. Drug. Deliv. Rev.* **175**, 113775 (2021).
188. Yáñez-Mó, M. et al. Biological properties of extracellular vesicles and their physiological functions. *J. Extracell. Vesicles* **4**, 27066 (2015).
189. Choi, H. Y. et al. Microparticles from kidney-derived mesenchymal stem cells act as carriers of proangiogenic signals and contribute to recovery from acute kidney injury. *PLoS ONE* **9**, e87853 (2014).
190. Kholia, S. et al. Mesenchymal stem cell derived extracellular vesicles ameliorate kidney injury in aristolochic acid nephropathy. *Front. Cell Dev. Biol.* **8**, 188 (2020).
191. Shi, Z., Wang, Q., Zhang, Y. & Jiang, D. Extracellular vesicles produced by bone marrow mesenchymal stem cells attenuate renal fibrosis, in part by inhibiting the RhoA/ROCK pathway, in a UUO rat model. *Stem Cell Res. Ther.* **11**, 253 (2020).
192. Grange, C. et al. Stem cell-derived extracellular vesicles inhibit and revert fibrosis progression in a mouse model of diabetic nephropathy. *Sci. Rep.* **9**, 4468 (2019).
193. Nassar, W. et al. Umbilical cord mesenchymal stem cells derived extracellular vesicles can safely ameliorate the progression of chronic kidney diseases. *Biomater. Res.* **20**, 21 (2016).

Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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