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Review

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Role of inflammation in the progression of diabetic kidney disease

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Abstract

Diabetic kidney disease (DKD) is a global health burden and the leading cause of end-stage renal disease. Its clinical management focuses on controlling hyperglycemia, hypertension, and hyperlipidemia. While the progression of DKD can be slowed with intervention, it cannot be stopped or reversed yet. The pathogenesis of DKD is complex, with an interplay of numerous signaling pathways, and research continues to decipher the players and their role, be it beneficial or pathogenic. Inflammation is an essential defense of our bodies against internal or external insults. The injuries that trigger inflammation range from pathogenic infections and wounds to dysregulated metabolism. Inflammation is helpful only if it is controlled and subsides after it has helped defend the individual against the insult. Uncontrolled or chronic inflammation is recognized as a contributor to numerous chronic diseases. Dysregulated inflammation plays a role in multiple aspects of DKD: glomerular hyperfiltration, mesangial expansion, podocyte injury, tubular injury, basement membrane thickening, fibrosis, and scarring. Since inflammation plays an integral role in the progression of DKD, targeting it for therapy is also reasonable. There is a growing trend of targeting inflammation as a therapeutic approach, with new targets being discovered and drugs evaluated every year. The exponential increase in literature necessitates a comprehensive summary of current information, hence this review.

Keywords: Diabetes, inflammation, diabetic nephropathy, DKD, CKD, fibrosis, oxidative stress

INTRODUCTION

The International Diabetes Federation estimates that 537 million adults have diabetes, and ~40% of them

develop DKD[1,2]. New cases of chronic kidney disease (CKD) in patients with T2DM or type-2 DKD increased by 74% between 1990 and 2017[2]. DKD is associated with a higher risk of cardiovascular events, kidney failure, and premature mortality[2-4]. The global health burden of DKD is expected to worsen, necessitating urgent action in policy-making and research. Diabetes prevention and control remain the primary goals of preventing DKD. Clinical management focuses on managing hyperglycemia, hypertension, and hyperlipidemia to slow progression[4]. Complete stoppage or reversal remains a goal.

Inflammation is an essential defense of our bodies against internal or external injury. Pattern recognition receptors (PRRs) sense pathogen-associated or damage-associated molecular patterns (PAMPs or DAMPs) and induce inflammatory signaling cascades, producing cytokines. These molecules act in an autocrine manner to enhance inflammatory signaling and in a paracrine manner to recruit and activate immune cells like macrophages, lymphocytes, and dendritic cells. This is followed by immune cell-mediated clearance of pathogens or damaged tissue. The final step of inflammation is its resolution, which re-establishes homeostasis[5]. The persistence of inflammatory inducers or inefficient resolution results in chronic inflammation causing oxidative stress (OS) and mitochondrial dysfunction (e.g., increased free radicals, advanced glycation endproducts (AGEs), and oxidized lipoproteins), further perpetuating inflammation in a feed-forward loop[6].

Although not the initiator, low-grade inflammation occurs in diabetes before the onset of DKD[7,8]. A chronic inflammatory state in a prediabetic individual can predict T2DM development[9]. Inflammation progresses alongside DKD, evidenced by the infiltration of immune cells in kidney biopsies and association studies showing the upregulation of inflammatory pathways[10-14]. Single-cell transcriptomic analyses corroborate immune-cell infiltration and upregulation of inflammatory pathways[15-17]. A chronic inflammatory insult to the kidney contributes to various structural and functional changes in DKD[18]. The kidney risk inflammatory signature (KRIS) comprising 17 circulating inflammatory proteins of a non-renal source relates to a higher risk of end-stage renal disease (ESRD) in patients with diabetes[19]. Other serum and urinary markers of renal and systemic inflammation correlate well with renal decline in T1DM- and T2DM-DKD[20,21], and they might predict the presence and prognosis of DKD[22].

We aim to review recent advances in research that help us better understand the role of inflammation in DKD. We describe how inflammation is intertwined in its pathogenesis and progression, followed by a review of the inflammatory pathways and players involved. Finally, we reflect on their therapeutic potential and future possibilities.

INFLAMMATION IN THE PATHOGENESIS OF DKD

DKD is a clinical diagnosis of persistent albuminuria (urinary albumin excretion (UAE) ≥ 30 mg/day or ≥ 30 mg/g) or persistent decreased estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m^2), or both, in patients with diabetes[23]. A biopsy is not usually required for diagnosis unless non-DKD is suspected. Pathological findings can be grouped under glomerular, vascular, and tubulointerstitial damage. Kidneys of T1DM patients predominantly develop classical glomerulopathy, characterized by glomerular basement membrane (GBM) thickening, mesangial expansion, podocyte loss, and glomerulosclerosis. Hyalinosis and sclerosis of the larger arteries are relatively common findings in type-1-DKD biopsies. Tubulointerstitial fibrosis usually follows glomerular damage and is soon followed by progression to ESRD. T2DM patients have more diverse pathological findings in their kidneys, with vascular and tubulointerstitial disease affecting some (esp. non-proteinuric DKD patients) more than glomerular damage[23,24].

DKD pathogenesis is multifactorial [Figure 1]. Hyperglycemia is the most well-researched and obvious trigger for diabetes and its associated complications. However, other metabolic derangements and hemodynamic abnormalities also contribute. Metabolic factors, like excess fatty acids, AGEs, and OS, activate inflammatory pathways[25,26]. Fructose exposure reduced lymphocyte subpopulations, increased DNA damage, and dysregulated immune-related genes, including mitogen-activated protein kinase 8 (MAPK8 or JNK1) and leukocyte-specific transcript 1 (LST1)[27]. A sugar-rich diet triggers a pro-inflammatory response via altering the gut microbiome and Toll-like receptor 4 (TLR4) signaling[28]. Superoxide and presumably other ROS activate TLR4 signaling and neutrophil NADPH oxidase (NOX) to form neutrophil extracellular traps (NETs)[29]. NETs are networks of extracellular fibers, mainly composed of neutrophil DNA, which trap and kill pathogens by engulfing them, producing antimicrobials, and saving host cells from damage. NETs increase in patients and murine models of DKD and correlate with DKD severity[30]. In sterile inflammation, NETs probably form to counter cell death and OS.

Similarly, hemodynamic abnormalities, such as hypertension-induced shear stress, microvascular changes resulting in hyperperfusion or hypoxia, and renin-angiotensin-aldosterone system (RAAS) activation, contribute to the complex network of pathogenetic events in the kidney, including an increase in growth factors, vasoactive hormones, and most relevant to this review, pro-inflammatory cytokines and chemokines[31,32].

An inflammatory response has the following contributors: inducers (infection, tissue damage, pathology), sensors (cells expressing PRRs), mediators (cytokines, chemokines), and the tissues that are affected[5]. In the context of the diabetic kidney, the inducers are hyperglycemia, AGEs, ROS, and DAMPs. All renal cell types express PRRs to sense pathological changes in their vicinity and act as inflammatory sensors. The mediators are not inherently different in the kidneys. The target tissues are the damaged cells and regions in the kidney that require repair. Next, we review the different spatiotemporal roles of inflammation in the progression of DKD pathology.

Glomerular inflammation

Damage to the renal glomeruli is considered one of the first events in DKD development, including GBM thickening, mesangial expansion, podocyte loss, and glomerulosclerosis. Podocytes and endothelial cells are responsible for maintaining the GBM, its charge barrier, and the shape and integrity of the glomerular capillary loop, which are all compromised in the diabetic glomerulus[32]. The diabetic milieu with numerous inflammatory inducers triggers the release of pro-inflammatory cytokines and activation of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) with a pyrin domain 3 (NLRP3) inflammasome in podocytes[33,34]. Induced podocyte-derived cytokines, like TNF-α, mediate monocyte differentiation and macrophage recruitment, contributing to glomerular injury and proteinuria[34]. Levels of serum amyloid A (SAA), a potent pro-inflammatory protein, increase in DKD patients and mice models correlating well with disease progression. Podocytes might be the primary renal cells that respond to the increased SAA by inducing nuclear factor-kappa B (NFκB) signaling[35].

Inflammation-mediated endothelial injury is multifaceted. NET inhibition by GSK484, a selective and reversible peptidyl arginine deiminase 4 (PAD4, a marker of NETs) inhibitor, ameliorates endothelial dysfunction in murine and human endothelial cells exposed to hyperglycemia[30]. Insulin-like growth factor-binding protein 5 (IGFBP5) is upregulated in DKD and enhances inflammation by metabolically reprogramming glomerular endothelial cells. Pro-inflammatory factors, like interleukin 6 (IL6), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein 1 (MCP1), and intercellular adhesion molecule 1 (ICAM1), are induced by IGFBP5, which itself is upregulated by hyperglycemia in endothelial

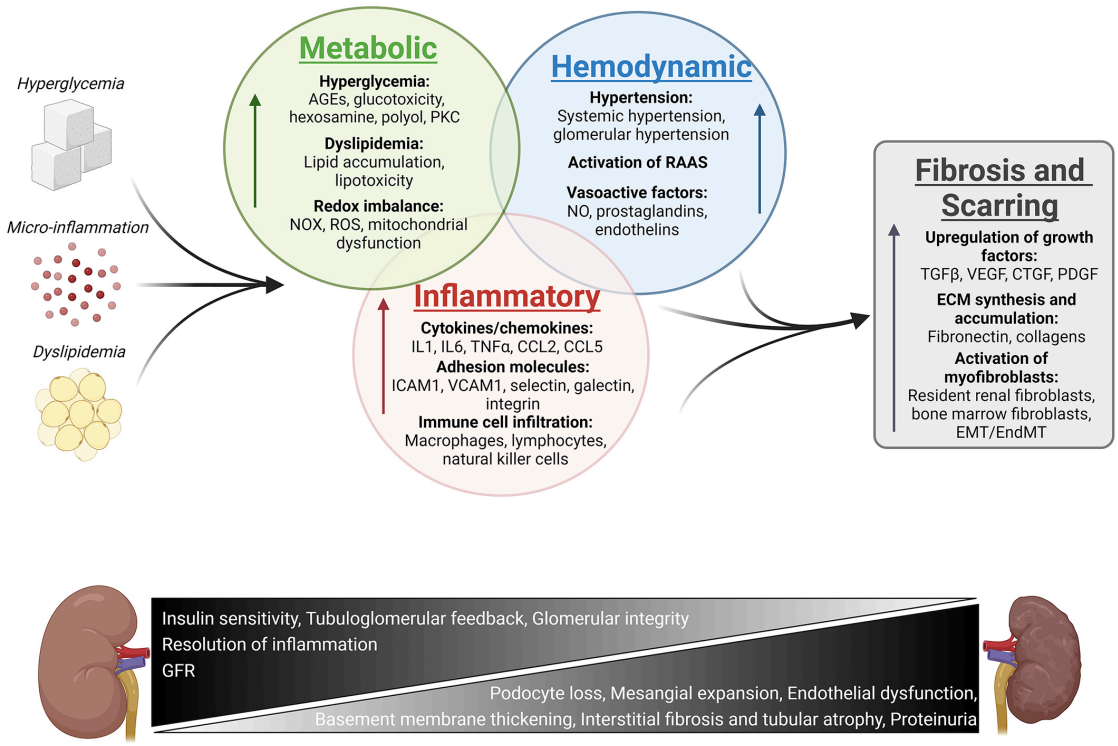

Figure 1. Pathogenesis and progression of DKD. The upper panel outlines the primary triggers of DKD in the diabetic milieu, viz. hyperglycemia, dyslipidemia, and microinflammation (a chronic low-grade inflammatory state can predict and predispose an individual to diabetes and DKD). These triggers induce several metabolic, hemodynamic, and inflammatory factors. The interconnected factors cause intracellular changes followed by progressively detrimental alterations to the renal architecture, leading to fibrosis, scarring, and functional decline, ultimately resulting in renal failure. The lower panel recounts pathophysiological changes with the progression of DKD. AGEs: Advanced glycation endproducts; CCL: CC motif chemokine ligand; CTGF: connective tissue growth factor; DKD: diabetic kidney disease; EMT: epithelial-to-mesenchymal transition; EndMT: endothelial-to-mesenchymal transition; GFR: glomerular filtration rate; ICAM: intercellular adhesion molecule; IL: interleukin; NO: nitric oxide; NOX: NADPH oxidase; PDGF: platelet-derived growth factor; PKC: protein kinase C; RAAS: renin-angiotensin-aldosterone system; ROS: reactive oxygen species; TGF: transforming growth factor; TNF: tumor necrosis factor; VCAM: vascular cell adhesion molecule; VEGF: vascular endothelial growth factor.

cells. This inflammatory action of IGFBP5 is dependent on its regulation of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), a glycolytic enzyme[36]. Suppressing PFKFB3-driven glycolysis restrains endothelial-to-mesenchymal transition and fibrotic response in cardiac endothelial cells. While this work focused on cardiac fibrosis, similar signaling might play a role in DKD renal fibrosis[37]. Allograft inflammatory factor-1 (AIF-1) is upregulated in glomerular endothelial cells in the diabetic kidney, and knocking it down ameliorates kidney inflammation and injury. AIF-1 enables glomerular endothelial cell inflammation and OS in DKD via NFκB signaling[38]. Panzer *et al.* showed the differential regulation of monocyte/macrophage recruitment in the glomerulus *vs* tubules: MCP1 was more important in the glomeruli and osteopontin in the tubular compartment[39].

The most characteristic of all diabetic glomerular changes is GBM thickening[32,40]. It starts well before DKD diagnosis, within a few years of diagnosis of diabetes. However, the thickening is more pronounced in DKD. Changes in the composition, charge, or architecture of the GBM associated with thickening could contribute to the pathogenesis of DKD. Stiffening of the GBM resulting from the thickening may also facilitate glomerular injury through hemodynamic mechanisms[31].

The mesangium undergoes numerous progressive changes with DKD: mesangial cell proliferation and hypertrophy, mesangial matrix expansion, and mesangiolysis[32,40]. USP25, a deubiquitinating enzyme, is upregulated in the mesangial cells and infiltrating macrophages in a diabetic kidney. It ameliorates DKD by inhibiting TRAF6-mediated inflammatory responses[41]. The expansion of the mesangium reduces the capillary surface area, contributing to glomerular hypertension and reduced glomerular filtration[32]. Thus, glomerular inflammation causes increased permeability of the filtration barrier. This allows proteins, like albumin, to leak into the urine, causing microalbuminuria and, subsequently, proteinuria, which is used for diagnosis and prognosis.

Vascular inflammation

Kidneys represent one of the most vascular organs in the body and, despite their relatively smaller size and weight, receive 25% of the cardiac output. Most serious long-term complications of diabetes, including DKD, are mediated by vascular involvement. Oxidative stress and inflammation affecting the renal vasculature play a crucial role in the development and progression of DKD [Figure 2]. Arteriolosclerosis and arteriolar hyalinosis that develop as a result of these intrarenal processes are essential structural changes that ultimately contribute to the progression of DKD. Vascular inflammation is a precursor to arteriolosclerosis. Recent studies underscore the significance of NLRP3 inflammasome activation, which may contribute to vascular inflammation in diabetes[42].

In diabetes, all cells are chronically exposed to high plasma glucose levels; however, some get affected more than others and manifest progressive dysfunction. Endothelial cells cannot lower their glucose transport in response to high glucose levels[43]. This results in much higher levels of intracellular glucose, which trigger the generation of inflammatory inducers and mediators that contribute to the development of diabetic complications, including DKD. Markers of inflammation like C-reactive protein (CRP), vascular cell adhesion molecule (VCAM), and IL1 correlate with microvascular complications in diabetic patients[44]. However, high glucose exposure can only cause inflammation in human vascular cells if primed with an inflammatory stimulus such as IL1β or TNF-α[45,46]. The excess intracellular glucose is diverted to the pentose phosphate pathway, providing additional substrate for NOX and increasing free radicals[47]. The pro-oxidant environment further exacerbates inflammation and tissue damage.

Hyperglycemia-induced endothelial dysfunction increases vascular susceptibility to shear, oxidative, and other stressors[47]. With subsequent microvascular rarefaction, it reduces blood flow, causing hypoxia. Renal hypoxia induces compensatory changes in blood flow, metabolism, and glomerular neoangiogenesis[32,48,49]. Decreased blood flow, impaired oxygen utilization by mitochondrial dysfunction, and microvascular thinning contribute to hypoxia and ischemia in the proximal tubular compartment[50-52]. AGEs also contribute to vascular complications of diabetes, mediated by methylglyoxal derivatives, which are metabolized by glyoxalase-1. Inducers of glyoxalase-1, such as t-resveratrol-hesperetin, have proven beneficial for DKD in preliminary trials by reducing insulin resistance and vascular inflammation[53]. NETs are usually formed in the vasculature near endothelial cells[30]. They can cause endothelial cell death and vascular necrosis[54,55].

Recent clinical observations revealed that a significant proportion of patients with DKD (~30%-40%) do not exhibit significant proteinuria. In these non-proteinuric DKD patients, vascular disease, particularly arteriosclerosis, is widely prevalent and often caused by inflammation. Vasoactive factors such as endothelin, nitric oxide, and angiotensin, along with inflammatory mediators such as NF-kB, peroxynitrite, and TNF-α, play a major role in vascular inflammation that leads to sclerosis.

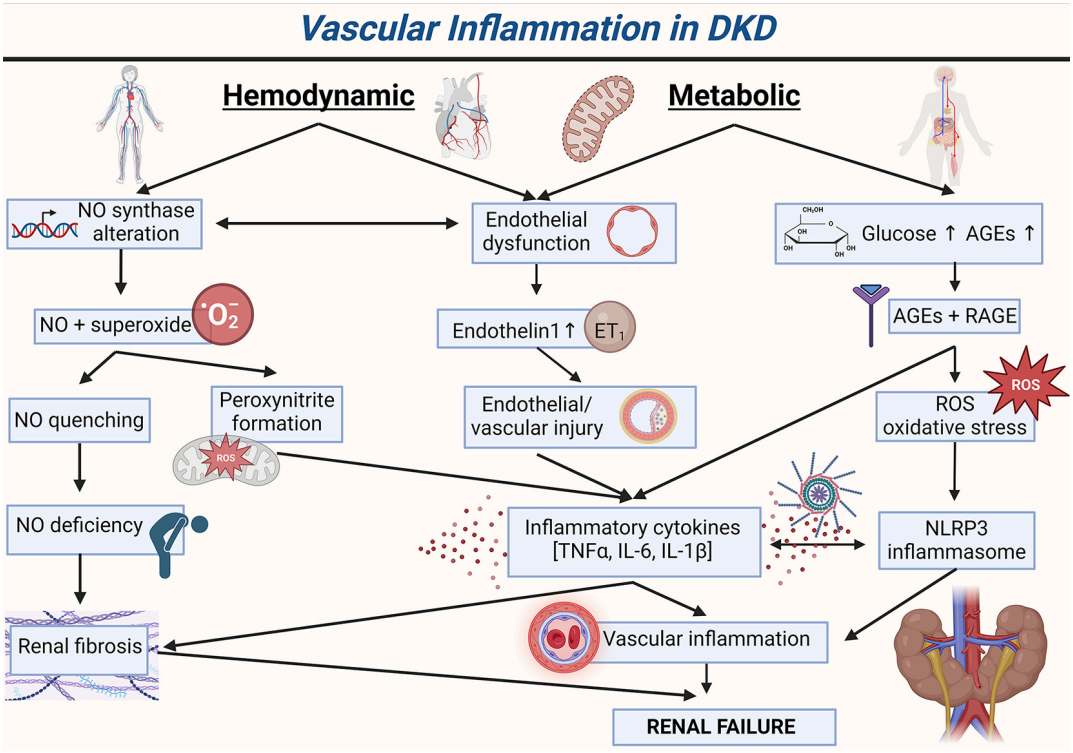

Figure 2. Vascular inflammation in DKD. The schematic illustrates the signaling pathways and mechanisms leading to vascular inflammation in DKD. Both hemodynamic and metabolic alterations in diabetes contribute to the activation of these pathways. While the nitric oxide pathway may be upregulated in the early phases of DKD and contribute to hyperfiltration, NO levels decrease as the course progresses, partly due to NO quenching by superoxide, leading to peroxynitrite, which stimulates inflammatory cytokines. Similarly, endothelin activation by hemodynamic and metabolic factors leads to endothelial injury and vascular inflammation. Chronic uncontrolled hyperglycemia leads to advanced glycation endproducts, which trigger inflammasome and oxidative stress. Ultimately, all the signaling alterations lead to vascular inflammation, contributing in a major way to renal demise in diabetes. AGEs: Advanced glycation endproducts; RAGE: receptor for AGE; TNF-α: tumor necrosis factor-alpha; IL: interleukin; NLRP3: NOD-like receptor family pyrin domain-containing 3; ROS: reactive oxygen species; NO: nitric oxide.

Tubulointerstitial inflammation

Inflammation is one of the primary triggers of tubulointerstitial injury during DKD, leading to fibrosis and functional loss. Tubulointerstitial lesions can precede or occur irrespective of glomerular lesions, as evidenced by normo-proteinuric or non-proteinuric DKD[56]. Impaired albumin uptake by proximal tubule cells might contribute to microalbuminuria, irrespective of glomerular damage[57]. Sustained hyperglycemia causes hypertrophy and proliferation in tubular epithelial cells, increasing reabsorption of glucose and sodium - the damage-causing stimuli. An aberrant tubuloglomerular feedback results in increased intraglomerular pressure and hyperfiltration. Thus, a more tubule-centric view of DKD is warranted[50,58].

High glucose exposure triggers MAPK and protein kinase C (PKC) signaling in renal tubular cells, stimulating the expression of pro-inflammatory molecules, such as IL6, MCP1, and osteopontin[39,59]. AGEs also trigger tubulointerstitial inflammation. Proximal tubules are the primary sites for AGE resorption and are induced in their presence to produce pro-inflammatory molecules (IL8, ICAM1)[50,60,61]. These cytokines and chemokines enable the recruitment and infiltration of immune cells like monocytes and macrophages in the renal tubulointerstitium, which further increases pro-inflammatory, profibrotic, and antiangiogenic factors, culminating in interstitial fibrosis and tubular atrophy (IFTA). The interstitial macrophage aggregation has prognostic value in DKD as it correlates well with the progression of the disease[62,63]. The expression of myostatin, a member of the transforming growth factor-beta (TGF-β) superfamily, increases

in DKD predominantly in the tubulointerstitium. It induces pro-inflammatory and profibrotic signaling (NFκB, CCL2, SMAD) in proximal tubules, suggesting its role in interstitial fibrosis in DKD[64].

Tubular epithelial cells typically prefer fatty acid oxidation (FAO) as an energy source; however, in DKD, FAO gets dysregulated, resulting in an increased dependence on glycolysis for energy and intracellular lipid deposition, which increases apoptosis and dedifferentiation[65,66]. High glucose and AGEs enhance cellular lipid synthesis and free fatty acid and cholesterol uptake, contributing to intracellular lipid accumulation, which fosters inflammation, OS, and endoplasmic reticulum stress[50,67,68]. Kidneys of type-2 DKD patients and murine models also show ectopic lipid deposits predominantly in the proximal tubular compartment. Sustained hyperglycemia increases the expression of adipose differentiation-related protein (ADRP) and sterol regulatory element binding protein 1 (SREBP1) in proximal tubule cells, along with other markers of tubulointerstitial damage. *In vitro* experiments indicate that they mediate tubular inflammation[69]. Perirenal fat accumulation is pathogenetic in DKD. Adipocytes secrete adipokines and cytokines, promoting inflammation and OS and mediating kidney function decline[70,71].

Since tubulointerstitial lesions could be the first pathology associated with DKD, biomarkers of tubular function might have diagnostic and prognostic value, e.g., serum levels of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), or urine levels of retinol-binding protein 4, cystatin C, and fatty acid binding protein 1[50,58].

Oxidative stress

OS and chronic inflammation are intertwined in DKD, each worsening the other in a slow feed-forward loop[72-74]. In one of the first reports suggesting a causal role of hyperglycemia in immune activation, Esposito *et al.* showed that acute hyperglycemia spikes circulating pro-inflammatory cytokine concentrations (IL6, IL18, and TNF-α) through an oxidative mechanism[75]. Reactive oxygen species (ROS) produced during inflammation directly damage renal cells and induce inflammatory signaling to recruit immune cells for repair, which causes more OS, thus completing the loop. Eventually, this progresses to fibrosis and endothelial dysfunction[75-77].

An imbalance between the producers and quenchers of ROS results in their accumulation. Numerous pathways contribute to ROS generation in diabetic kidneys, e.g., the uncoupling of nitric oxide synthases (NOS), NOX, advanced glycation, and mitochondrial dysfunction[73,78-80]. Hyperglycemia triggers mitochondrial dysfunction and superoxide release in glomerular endothelial cells, which secrete factors to initiate podocyte apoptosis[81].

Programmed cell death (PCD) mechanisms of apoptosis, autophagy, and necroptosis play important roles in DKD, especially in damaged podocytes and proximal tubule cells[82]. Recently, the focus has increased on ferroptosis, an iron-dependent form of PCD, in the pathogenesis of DKD[83]. ROS-induced autophagy promotes intracellular iron accumulation and ferroptosis[84]. Hyperglycemia and inflammation trigger ferroptosis in renal endothelial and tubular cells, reducing their viability and contributing to endothelial and tubular dysfunction in DKD[85,86]. Iron accumulation, lipid peroxidation, and decreased antioxidant activity - processes that drive ferroptosis - increase in renal tubular cells cultured in high glucose, and upregulating the protective antioxidant signaling reduces diabetes-related ferroptosis, delaying DKD progression[86,87].

Pathogenesis of DKD is inseparable from ROS overactivation. While a significant contributor to DKD, antioxidants have not fared well in clinical trials for DKD, but whether they amplify the effect of other therapies remains to be seen.

Immune cell infiltration

Bioinformatic studies are revealing the changes in the landscape of immune cells in the DKD kidney. More memory B cells, T cells, activated natural killer (NK) cells, macrophages, resting dendritic cells, and resting mast cells were found in the glomerulus of patients with DKD, with fewer naïve B cells, resting NK cells, activated mast cells, and neutrophils[88]. With pooled samples of glomerular and tubular DKD data sets, Wang *et al.* verified more macrophages and fewer Treg and Th2 cells in diabetic kidneys. Immune cells were identified primarily in the interstitium compared with the glomeruli[89]. Pathway analyses show activation of leukocyte trans-endothelial migration, T-cell receptor signaling, NOD-like receptor signaling, chemokine signaling, cell adhesion molecules, extracellular matrix (ECM) receptor interaction, and phagocytosis[88,89]. Using single-cell RNA sequencing followed by verification in human patient biopsies, Fu *et al.* focused on changes in macrophage dynamics with DKD progression[15]. With a similar technique, Wilson *et al.* focused on the changes in the signaling landscape among the different cell types in the kidney during early DKD. They found the expected 7- to 8-fold increase in leukocytes (attributed to infiltration). They note cell type-specific changes in gene expression that are important for immune cell activation, reinforcing the thought that inflammation is not a passive byproduct; instead, different types of renal cells might actively contribute to its induction[17].

Fibrosis and scarring

Prolonged inflammation triggers kidney fibrosis - a hallmark manifestation in progressive CKD, irrespective of the primary insult. Deregulated wound healing leads to excessive production and accumulation of ECM proteins, such as fibronectin and collagens[90]. When kidneys are injured, local fibroblasts and pericytes are activated, increasing their contractility, secreting inflammatory mediators, and synthesizing ECM components, which trigger wound healing. However, when the damage is repetitive (e.g., DKD), the ECM proteins accumulate in the parenchyma, resulting in tissue disruption, renal dysfunction, and organ failure[91,92].

Fibrosis in the DKD kidney is indicated by the presence of tubule atrophy, chronic interstitial inflammation and fibrogenesis, glomerulosclerosis, and vascular rarefaction. Renal function and prognosis correlate better with tubulointerstitial fibrosis than early glomerular changes[93]. A complex interaction ensues between the injured renal parenchyma (tubular cells) and multiple non-parenchymal cells (immune and mesenchymal cells) within the scarring areas. Wang *et al.* implicated the role of sonic hedgehog (Shh) secreted from senescent tubular cells along with other senescence-associated proteins in fibroblast activation and proliferation in DKD[94]. Several sources contribute to the accumulation of activated myofibroblasts in different proportions: transformation of the resident fibroblasts and mesenchymal stem cells, recruitment of fibroblasts from the bone marrow, epithelial-to-mesenchymal transition (EMT) of tubular epithelial cells[91,92].

PATHWAYS

NFκB pathway

NFκB regulates the expression of the primary mediators of inflammation. Sensing PAMPs or DAMPs, PRRs activate a signaling cascade that culminates in freeing NFκB from its inhibitor IκB (inhibitor of NFκB) to translocate to the nucleus and activate target gene expression [Figure 3]. IκB is a target of NFκB; this allows for quick and transient activation of this pathway[95,96].

All resident kidney cells possess the capability of activating NFκB. It is rapidly activated by diverse stimuli, including hyperglycemia, AGEs, mechanical stress, ROS, inflammatory cytokines, and angiotensin II - all present in excess in the diabetic milieu. Activated NFκB stimulates the transcription of pro-inflammatory cytokines, chemokines, and adhesion molecules[95,97]. The activation of NFκB and its targets correlates with

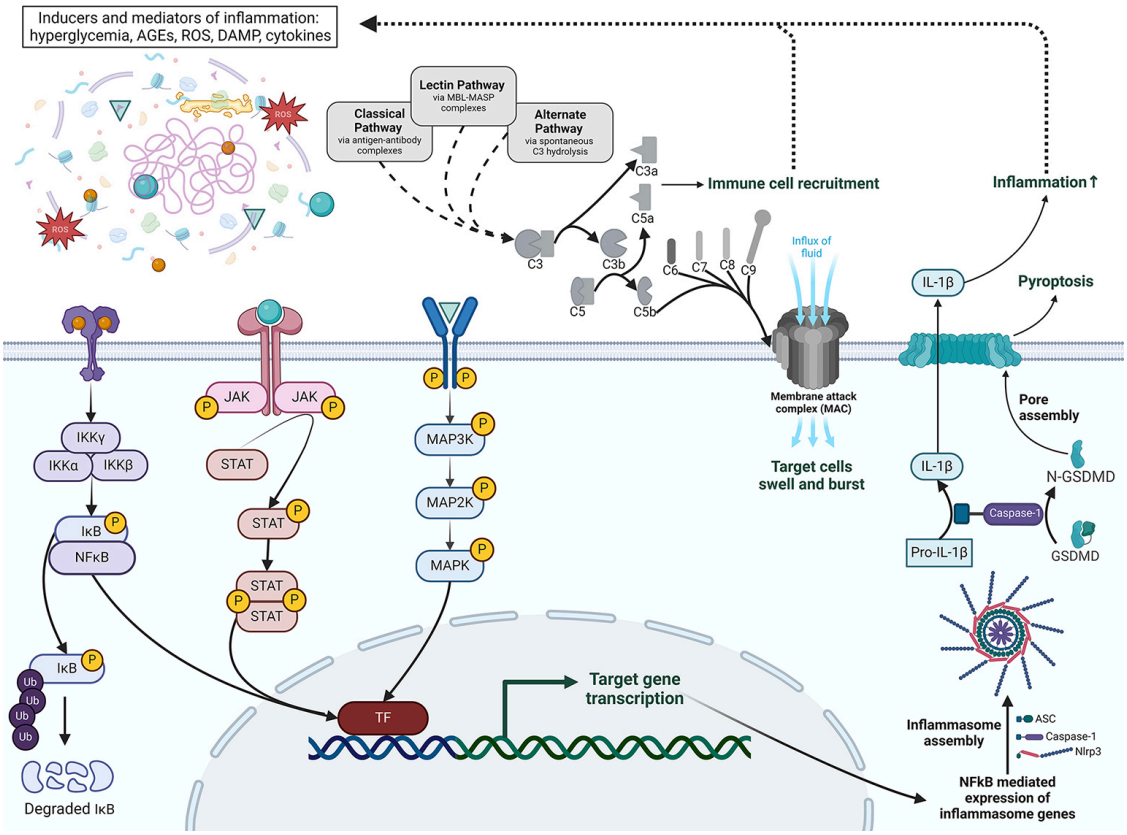

Figure 3. Inflammatory signaling pathways in DKD. The schematic summarizes the inflammatory signaling pathways that drive DKD. From left to right: NFκB pathway, JAK/STAT pathway, MAPK pathway, complement cascade, inflammasome signaling. NFκB remains inhibited and retained in the cytosol under physiological conditions. Activated pattern recognition receptors activate the IKK complex, which phosphorylates IκB, causing its degradation and freeing NFκB to translocate to the nucleus and activate target gene expression. Cytokine receptors dimerize upon detecting their cytokines, leading to transactivation of the associated JAKs. Activated JAK recruits and phosphorylates the transcription factor STAT, which then dimerizes and activates its target gene expression. MAPK pathway is a phosphorylation cascade resulting in activated MAPK translocating into the nucleus and transcribing target genes. When triggered, the complement system results in a cascade of proteolytic enzymes culminating in the formation of membrane attack complex and pro-inflammatory mediators. NFκB mediates the assembly of inflammasomes, which in turn release pro-inflammatory inducers and mediators. AGEs: Advanced glycation endproducts; DAMP: damage-associated molecular patterns; GSDMD: gasdermin D; IKK: IκB kinase; IL: interleukin; IκB: inhibitor of NFκB; JAK: Janus kinase; MAP2K: mitogen-activated protein kinase kinase; MAP3K: mitogen-activated protein kinase kinase kinase; MAPK: mitogen-activated protein kinase; MASP: MBL-associated serine protease; MBL: mannose-binding lectin; NFκB: nuclear factor kappa B; ROS: reactive oxygen species; STAT: signal transducer and activator of transcription; TF: transcriptional factor; Ub: ubiquitin.

the degree of tubular damage and can indicate renal damage progression in DKD patients[98]. Tubular injury in patients with DKD correlates with TLR4 upregulation. TLR4/NFκB signaling induces gasdermin D-mediated pyroptosis in tubular cells in DKD[99] [Figure 3]. In experimental murine models of DKD, the TLR-NFκB pathway is chronically active and promotes glomerular injury. Chronic treatment with an NFκB inhibitor prevented the expression of the disease (glomerular injury, inflammation, and oxidative stress)[38,100].

JAK/STAT signaling

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a key signaling node in DKD progression [Figure 3]. Inhibitory regulators of this pathway include the constitutive protein inhibitors of activated STAT (PIAS) and protein tyrosine phosphatases (e.g., PTP1B) and the inducible suppressors of cytokine signaling (SOCS). The constitutive presence of inhibitors allows for a transient

activation of this pathway. The JAK/STAT pathway is activated by a range of metabolism-related cytokines and hormones, such as IL3, IL6, and angiotensin II[101-103].

JAK/STAT signaling is implicated in multiple aspects of DKD: inflammation, fibrosis, RAAS, autophagy, and EMT[101,103-107]. Higher levels of JAK2 are seen in the glomerular and tubulointerstitial compartments of DKD-patient kidneys. Upregulation of JAK1-3, STAT1, and STAT3 were seen in DKD patients with eGFR significantly correlating with tubulointerstitial JAK1-3 and STAT1 expression[108]. Genetic mutants of STAT3 in mice show that IL6-mediated activation of STAT3 is required for diabetic glomerulopathy development. STAT3 knockdown reduced STAT3 phosphorylation and inflammatory marker expression, including IL6, MCP1, activated NFκB, type IV collagen, TGF-β, and ICAM1[101]. Chen *et al.* found that hyperglycemia activated JAK/STAT signaling, inhibited autophagy, increased podocyte apoptosis, and aggravated renal injury. Inhibiting the pathway by ruxolitinib, a JAK inhibitor, reversed the decrease in autophagy[106]. A protective role of Forkhead box 1 (FOXO1) on proximal tubule injury in DKD is mediated via JAK/STAT inhibition. FOXO1 downregulation increased the expression of pSTAT1, activated EMT, and initiated the intrinsic apoptotic pathway. Increasing FOXO1-mediated STAT1 inhibition alleviated tubulointerstitial fibrosis, tubular EMT, and apoptosis[109]. SOCS3 overexpression can reduce AGE-induced EMT by inhibiting the JAK2/STAT3 signaling in proximal tubule cells[107].

Members of this pathway are being considered for their therapeutic potential in DKD. Treatment with baricitinib (JAK1/JAK2 inhibitor) improved proteinuria and levels of biomarkers of inflammation in urine and blood (urine C-X-C motif chemokine 10 and urine C-C motif ligand 2, plasma soluble TNF receptors 1 and 2, ICAM1, and SAA) of subjects with DKD[110]. El-Kady *et al.* showed that ruxolitinib improved proteinuria, renal inflammation, and fibrosis in a rat model of T1DM[111].

MAPK pathway

MAPKs, a family of serine/threonine kinases, function through three pathways: the extracellular signal-regulated kinase (ERK)-MAPK, p38-MAPK, and Jun N-terminal kinase (JNK)-MAPK pathways. Initiated by an external stimulus, such as high glucose, MAPKKK phosphorylates MAPKK, which phosphorylates and activates MAPK to translocate into the nucleus and transcribe target genes[112] [Figure 3]. MAPK targeting shows promise, with several studies claiming that pathway inhibition alleviates DKD. For example, MAPK inhibition can reverse KIM-1-mediated macrophage M1 transformation and migration[113]. Antioxidant treatment reduces MCP1 and phosphorylated JNK levels in mesangial cells, reducing inflammation[114]. Blocking JNK signaling inhibits interstitial myofibroblast accumulation. JNK1/2 deletion does not inhibit renal fibrosis; however, JNK1 deletion decreases renal tubular apoptosis[115]. Inhibiting the ERK pathway reduces nitrite levels in stimulated macrophages by decreasing TNF-α production. ERK stimulates, and p38 inhibits, inducible NOS (iNOS, an inflammatory mediator)[116]. ERK and p38 also correlate with glomerular and tubulointerstitial lesions in patients with DKD[117].

p38 is activated in hyperglycemic conditions within podocytes, mesangial cells, and tubular cells, coinciding with TGF-β[118,119]. p38 expression is elevated in early diabetes with increased MAPKK3/6 and cAMP-responsive element binding protein (CREB) and is associated with renal hypertrophy and fibrosis[120]. p38-dependent CREB activation can mediate angiotensin II and lipoxygenase-induced fibronectin expression and cellular growth in mesangial cells[121]. p38 inhibition diminishes albuminuria in T1DM mice. p38 might regulate nephrin endocytosis in podocytes, as its inhibition leads to a loss of nephrin. p38 is phosphorylated at Ser1146 in diabetic mice, which then interacts with nephrin, leading to its endocytosis[119].

Complement cascade

The complement system is an innate immune defense mechanism and immune-metabolic regulator. It is a cascade of plasma proteins activating the next protein by proteolytic cleavage to induce inflammatory responses. Complement activation occurs by classical, alternative, and lectin pathways, with the latter triggered by the binding of lectins, such as mannose-binding lectin (MBL), to aberrant carbohydrates expressed on the surface of damaged cells. All three pathways converge at complement 3 (C3), which initiates an enzymatic cascade to generate the effector molecules, including C3a, C5a, and C3b, and ultimately, the membrane attack complex (MAC), forming pores in the target cell membranes, thereby killing them. C3a and C5a are potent pro-inflammatory mediators[122,123] [Figure 3].

The complement system is activated in DKD[10,123-126]. Hyperglycemia results in glycated proteins, which can directly activate the complement system by binding MBL and initiating pro-inflammatory signaling. Circulating MBL level is a robust biomarker for the development and progression of DKD[125,127]. Growing evidence suggests that MBL, C3, and MAC contribute to renal injury in the hyperglycemic milieu[123,128,129]. Antagonists of C5a and C3a receptors improve kidney fibrosis in diabetic rats[124].

NLRP3 inflammasome

Large protein complexes (> 700 kDa) containing caspase-1, apoptosis-associated speck-like protein (ASC), and NLRP3 form within stimulated immune cells such as monocytes, macrophages, and dendritic cells. These are called inflammasomes. On detecting danger signals, such as microbial motifs or DAMPs, NLRP3 assembles the NLRP3 inflammasome, causing caspase-1-dependent pro-inflammatory cytokine release and pyroptosis[130,131] [Figure 3]. The hyperglycemic milieu of DKD contains a surplus of stressors required for the assembly and activation of NLRP3 inflammasome. Inflammatory inducers activate NFκB signaling, expressing and activating NLRP3, pro-IL1β, and pro-IL18, and transcriptional protein modifications such as ASC phosphorylation and NLRP3 deubiquitination. A secondary stimulus, like ROS, activates the inflammasome by oligomerizing inactive NLRP3 and activating pro-caspase-1[130].

Podocyte-specific NLRP3 inflammasome activation is necessary and sufficient for the expression of DKD in hyperglycemic mice. Podocyte-specific NLRP3 gain-of-function mutant aggravated hyperglycemia-induced kidney damage (albuminuria, mesangial expansion, and GBM thickening), whereas loss of NLRP3 or caspase-1 was renoprotective[33]. NETs promote NLRP3 inflammasome activation and glomerular endothelial dysfunction under hyperglycemic stress[30]. Inhibiting NLRP3 prevents hyperglycemia-induced lipid accumulation in podocytes and, therefore, podocyte damage[132]. Thus, NLRP3 inflammasomes exacerbate inflammation by promoting the release of pro-inflammatory cytokines, and sustained activation contributes to renal inflammation, fibrosis, and kidney damage.

Wnt/β-catenin

Essential for embryonic development, the Wnt/β-catenin pathway plays a role in DKD and impacts inflammatory pathways, such as NFκB and JNK[133-145] [Figure 4]. Snail, a Wnt target, is a marker of EMT and is associated with inflammation. During EMT, TNF-α triggers Snail and inhibits its ubiquitination[136,145]. Snail knockout in tubular cells displays lower macrophage infiltration and NFκB signaling, indicating that Wnt signaling mediates tubular inflammation[145]. IKKα plays a role in β-catenin target gene expression. TGF-β-mediated Wnt/β-catenin activation leads to increased binding between IKKα and β-catenin[143]. JNK binds to the E-cadherin/β-catenin complex as DKD progresses, showing JNK to be a player in EMT during DKD. JNK phosphorylates β-catenin and remodels the actin cytoskeleton[144].

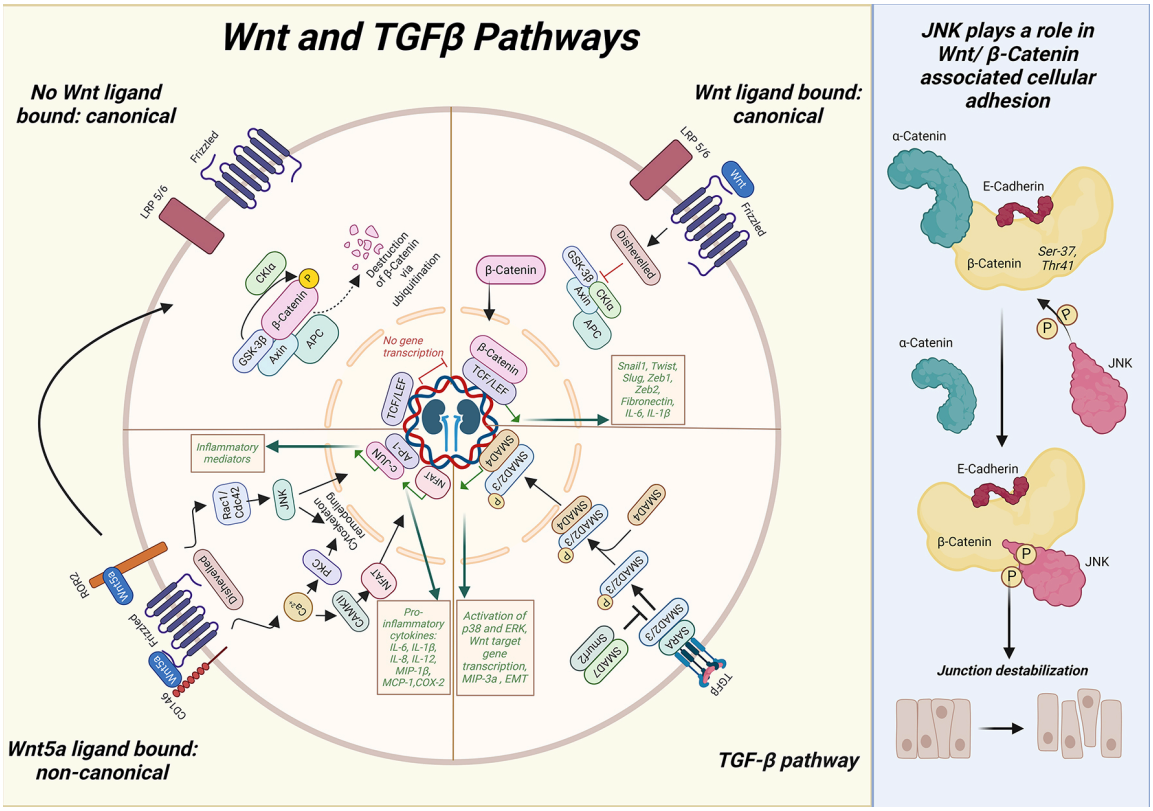

Figure 4. Wnt and TGF-β signaling pathways. To the left of the figure, Wnt canonical and non-canonical pathways are demonstrated. The top left of the sphere features the canonical Wnt/β-Catenin pathway with no ligand bound, leading to the formation of the β-Catenin destruction complex. The top right of the sphere shows the canonical Wnt/β-Catenin pathway when a ligand is bound, allowing target genes to be transcribed, many of which promote fibrosis and EMT. This is achieved by accumulating β-Catenin through the inhibition of the destruction complex. The bottom right showcases the TGF-β pathway which moves through SMAD proteins and interacts closely with both the Wnt/β-Catenin pathway and other traditional inflammatory pathways. Lastly, the bottom left of the sphere shows what is occurring in the Wnt non-canonical pathways when the pro-inflammatory Wnt5a ligand is bound. Non-canonical signaling involves the Ca+ pathway and the PCP (Planar Cell Polarity) pathways. The non-canonical pathways are much more complex than canonical signaling and involve interactions with other pathways through players such as NFAT, PKC, and JNK. This can also lead to inhibition of β-Catenin accumulation. To the right of the figure, phosphorylation interactions between JNK with β-Catenin, specifically at Ser-37 and Thr-41, leads to the destabilization of junctions in the context of cellular adhesion and motility. This is due to the loss of α-Catenin when JNK is bound to the respective residues. AP-1: Activator protein 1; APC: adenomatous polyposis coli; CD146: cluster of differentiation 146; Cdc42: cell division control protein 42; CKIα: casein kinase I alpha; GSK-3β: glycogen synthase kinase 3 beta; JNK: c-Jun N-terminal kinase; LEF: lymphoid enhancer-binding factor; NFAT: nuclear factor of activated T cells; PKC: protein kinase C; Rac1: Ras-related C3 botulinum toxin substrate 1; ROR2: receptor tyrosine kinase-like orphan receptor 2; SARA: SMAD anchor for receptor activation; TCF: T-cell factor; TGF-β: transforming growth factor-β.

Multiple RAAS players are direct targets of Wnt/β-catenin signaling. Inhibiting β-catenin in a mouse model of CKD led to a significant reduction in proteinuria, suggesting an interaction between RAAS and Wnt/β-catenin signaling in inflammation[140-142].

The Wnt/β-catenin pathway also impacts macrophage accumulation in the kidneys. In human, animal, and cell models, Wnt5a binds CD146, inducing non-canonical signaling-mediated TNF-α, IL6, and CCL2[138]. Stimulated human peripheral blood mononuclear cells (PBMCs), Wnt5a triggers non-canonical signaling-mediated macrophage activation. Silencing Wnt5a decreases inflammation[139]. A co-culture of chemokine-producing myeloid cells and early myofibroblasts exhibited β-catenin nuclear translocation during EMT. Blocking Wnt reduced β-catenin nuclear translocation, preventing EMT[146].

TGF-β/SMAD

TGF-β, a profibrotic factor, drives EMT within the kidney via SMAD proteins[147] [Figure 4]. Inhibiting the pathway suppresses renal fibrosis via expressing micro-RNA-29 (miR-29) and repressing miR-192 and miR-21[148]. The three TGF-β isoforms in the kidney, TGF-β1-3, are all profibrotic and promote matrix protein accumulation. TGF-β1 partially mediates TGF-β2 and TGF-β3 activity. However, different phases of nephropathy can exhibit other dominant isoforms, as TGF-β2 is dominant in the acute phase of streptozotocin-induced DKD[149].

Urinary levels of TGF-β can be a marker for IgA nephritis and glomerulosclerosis, as patients with these disorders have higher levels of urinary TGF-β and lower TGF-β receptors[150,151]. TGF-β is also correlated with the progression of interstitial fibrosis[150]. In rats with ischemia-reperfusion injury, inhibiting the TGF-β pathway via pirfenidone demonstrates renoprotective effects by relieving inflammation and fibrosis[152]. While inhibiting all three TGF-β isoforms alleviates renal fibrosis in rats, no clinical trials targeting TGF-β have succeeded[152,153].

Hyperglycemia-driven macrophage inflammatory protein-3a (MIP-3a) induction in renal proximal tubules is TGF-β1-dependent[154]. TGF-β is important for mitochondrial quality control in the proximal tubules. In mice, deleting TGF-β receptor 2 (TbR2) impairs mitochondrial complex 1, reducing quality control and increasing inflammation, promoting oxidative stress[151]. TGF-β null mice develop autoimmune disorders, while TbR2 deficiency induces a lethal inflammatory disorder 8-10 weeks following induction. When bone marrow from TbR2 deficient mice is transferred to healthy mice, the mice encounter inflammation and death[155]. Contrastingly, in mouse matrix-producing interstitial cells (MPICs), deletion of TbR2 did not significantly impact renal fibrosis during unilateral ureteral obstruction (UUO) and aristolochic acid-induced nephropathy. Collagen production was diminished, suggesting that there are complex mechanisms involved in TbR2 regulation[156]. TGF-β is pertinent for inflammation and can initiate Wnt target gene transcription and activate p38 and ERK[145].

PLAYERS

Numerous factors in the diabetic milieu induce inflammation: hyperglycemia[25,47,59,154,157], hyperlipidemia[158-160], reactive oxygen species[74,77,78,121], AGEs[68,107,161], and hypertension[162-164], to name a few. Chronic low-grade inflammation damages tissue, resulting in the production of DAMPs, which exacerbate inflammation.

Damage-associated molecular patterns

DAMPs are endogenous non-microbial inflammation inducers. Released from damaged cells, these danger molecules bind PRRs, activating inflammatory cascades to start the repair process. As expected, DAMPs can be pathogenic in inflammatory diseases[165,166]. DAMPs originate from different compartments: the extracellular matrix, such as fibronectin and tenascin C; different intracellular compartments, such as nuclear high-mobility group box 1 (HMGB1) and histones, cytosolic uric acid and heat shock proteins (HSPs), and mitochondrial DNA and ROS; and plasma proteins, like fibrinogen and SAA[166].

Detectable in the urine of patients with glomerular disease, soluble fibronectin induces chemokine expression in tubular cells by activating Src tyrosine kinases, ERK1/2, and NFκB[167]. Tenascin C promotes the proliferation of kidney interstitial cells via STAT3 activation[168]. When released to the extracellular space, HMGB1 (a redox-sensitive DNA chaperone) induces inflammation by binding to TLR2, TLR4, and RAGE[169]. Hyperuricemia is a common finding in DKD. Uric acid activates the immune system and affects resident kidney cells toward a pro-inflammatory and profibrotic state[170,171]. SAA, a clinical marker for active

inflammation, binds to and activates multiple PRRs (TLR2, TLR4), increasing NFκB activity and inflammatory mediators[35,166]. Several DAMPs are compelling candidates as biomarkers and therapeutic targets for DKD.

Pattern recognition receptors

Present primarily on the surface of immune cells, PRRs detect microbes or tissue damage by binding to specific molecular structures (PAMPs or DAMPs) and induce signaling cascades to produce inflammatory mediators. With chronic inflammation driving DKD, it is natural that PRRs play an essential role, and mounting evidence verifies this.

TLR2 and -4 are expressed on the surface of renal tubular epithelial cells, endothelial cells, podocytes, and mesangial cells and are implicated in mediating inflammation in these compartments in DKD[172-174]. Enhanced TLR4 expression and signaling were reported in renal glomeruli and tubules of patients with type 2 DKD and microalbuminuria. A 6-year follow-up of patients with microalbuminuria showed an association between enhanced glomerular TLR4 expression and renal functional decline[175]. TLR2 is likely the predominant long-term mediator of NFκB-dependent inflammation in proximal tubules[173]. The absence of TLR2 attenuates the pro-inflammatory state in a type 1 DKD mouse model[176].

NLRs, the other major PRRs, are present in the cytosol and sense intracellular PAMPs and DAMPs. NLRP3 is the most researched NLR in diabetes and DKD. NLRP3 oligomerizes to form inflammasome complexes with the adaptor protein ASC and the effector protein pro-caspase 1 (see Section "NLRP3 inflammasome"). Several triggers activate NLRP3, including fatty acids, uric acid, extracellular ATP, hyperglycemia, SAA, and mitochondrial ROS[157]. NLRP3 inflammasome exacerbates inflammation in glomerular endothelial cells and podocytes, as reviewed before[30,33]. Kim *et al.* describe an inflammasome-independent role of NLRP3 in renal tubular cells in mitochondrial ROS production in acute hypoxic renal injury[177]. The contribution of such mechanisms in CKDs remains to be seen.

AGEs are non-enzymatically glycated proteins, lipids, and nucleic acids, and their accumulation increases in diabetes[60]. AGE accumulation in the kidneys upregulates the expression of its receptor (RAGE)[178]. AGE-RAGE induces inflammation and oxidative stress and promotes fibrosis in the diabetic kidneys via canonical pro-inflammatory and profibrotic signaling, like NFκB, MAPK, and TGF-β/SMAD, contributing to DKD pathogenesis. Targeting AGEs/RAGE by pharmacotherapy, anti-glycating agents, or diet improves DKD[60,179].

MBL, a PRR, activates the lectin pathway of the complement system upon recognizing PAMPs or altered self-antigens. High MBL increases the risk of proteinuria and all-cause mortality in T1DM and T2DM[125,180,181]. A large-scale study reported a U-shaped association of serum MBL levels with cardiovascular events and all-cause mortality in T2DM, suggesting that low and high serum MBL expression are risk factors[182]. This makes sense when one sees inflammation playing a protective role and deregulated inflammation as damaging. MBL might, therefore, have predictive and prognostic value in DKD, but more studies are required[127,183].

Pro-inflammatory mediators

Cytokines are small secreted polypeptides that stimulate the movement of immune effector cells toward the sites of inflammation, infection, or trauma. Cellular communication mediated by cytokines can be autocrine or juxtacrine for signal amplification or paracrine to recruit blood-borne immune effector cells. Produced in response to infection or trauma via inflammatory signaling, cytokines recruit, stimulate, and proliferate

immune cells. Examples include ILs, chemokines, interferons, and TNFs. They are subdivided based on the nature of their function in the immune response. Pro-inflammatory cytokines perpetuate inflammation and are necessary in the initial stages of an inflammatory response, while anti-inflammatory cytokines control pro-inflammatory cytokines. Cytokines have long been implicated in the progression of DKD with prognostic and therapeutic implications[184].

Pro-inflammatory cytokines

Numerous cell types in the kidney can synthesize inflammatory cytokines, including the resident renal cells (glomerular, endothelial, tubular, and mesangial cells) and blood-borne cells. The production of these cytokines increases as nephropathy progresses, with an independent relationship found between these inflammatory molecules and kidney function[21,95,185-188].

Elevated levels of IL6 and CRP, representing an ongoing metabolic storm, are risk factors for T2DM in apparently healthy adults[8,9]. Patients with T2DM have higher levels of circulating pro-inflammatory cytokines (IL6, TNF-α), indicating a continued inflammatory state[7,72,189,190]. Moreover, hyperglycemia acutely increases circulating pro-inflammatory cytokine concentrations, and this effect is more pronounced in subjects with impaired glucose tolerance, thus confirming a direct causal effect of hyperglycemia in activating the immune system in diabetes[75]. Urinary and serum levels of pro-inflammatory cytokines IL1α, IL8, and IL18 correlate with biomarkers of podocyte damage (podocalyxin, synaptopodin, nephrin) and of proximal tubular dysfunction (KIM-1, NAG) in the early stage of DKD in T2DM[191]. IL1β, a macrophage-derived pro-inflammatory cytokine, stimulates the proliferation of renal fibroblasts and increases fibronectin and collagen production in a TGF-β-dependent mechanism, suggesting its role in renal fibrosis[192]. TNF-α contributes to the pathogenesis of DKD by regulating immune cells and cytokine release, as well as directly inducing ROS production[18,193]. Thus, pro-inflammatory cytokines perpetuate inflammation, further damaging the kidney tissue and contributing to kidney injury and fibrosis.

Chemokines

Chemokines and their receptors promote inflammatory cell interactions and recruitment to the injury site. High glucose and inflammatory cytokines increase the expression of MCP1 [also known as CC motif chemokine 2 (CCL2)] in mesangial and tubular cells[98,194]. Serum MCP1 levels correlate with albuminuria and are an independent risk factor for developing type 2 DKD[195]. Urinary levels of MCP1 correlate with UAE and eGFR[196]. Both serum and urinary levels of MCP1 can be diagnostic and prognostic biomarkers of DKD. Another potent chemoattractant for monocytes, macrophages, granulocytes, and T cells, CCL5 (also known as RANTES), correlates with proteinuria. It is produced in various renal cells, including fibroblasts, mesangial, and tubular cells, when induced by RAAS activation, pro-inflammatory cytokines, and protein overload[18,95,98]. A type 1 DKD animal model shows increased expression of fractalkine (CX3CL1) and its receptor[197]. Together, they mediate ECM production in mesangial cells and hypertension-induced interstitial fibrosis[198,199].

Adhesion molecules

Cell adhesion molecules aid the migration and homing of immune effector cells, like macrophages, to the kidney. Overexpression of cell adhesion molecules, such as ICAM1 and VCAM1, on the surface of endothelial and tubular cells aids in their capture of circulating macrophage precursors and leucocytes[36,200,201]. Glomerular hyperfiltration rather than hyperglycemia triggers the increase in ICAM1 expression in the early stages of DKD. Mononuclear cell infiltration into diabetic glomeruli is prevented by anti-ICAM1 antibody[201]. AGEs induce upregulation of ICAM1 expression in tubular and mesangial cells[61,202]. VCAM1 is another adhesion molecule implicated in immune cell infiltration in DKD. VCAM1

expression increases in endothelial, tubular, and infiltrating cells in the renal interstitium in a diabetic state[200,203]. Circulating VCAM1 levels increase and correlate with UAE in patients with T2DM[204].

Anti-inflammatory mediators

An inflammatory response is supposed to aid the organism in healing from a pathological insult or injury, but its dysregulation causes it to become an insult. The balance between pro- and anti-inflammatory mediators dictates the overall effect of inflammatory response.

Anti-inflammatory cytokines

Pro-inflammatory cytokines initiate the early responses and amplify inflammatory reactions, whereas anti-inflammatory cytokines, including IL4, IL10, IL11, and IL13, have the opposite effect in that they limit the pro-inflammatory cytokine response[205]. A mouse model of albumin overload-induced tubulointerstitial injury showed that IL4 receptor alpha (IL4Rα) is upregulated in the proximal tubule cells via JAK3/STAT6 signaling. Suppressing IL4 signaling in these cells reverses the inhibitory effect of higher albumin concentration without changing albumin endocytosis[206]. Whether IL4 signaling may play a protective role in DKD remains to be seen.

A recent systematic review found an inverse relationship between IL10 levels and oral disease in patients with diabetes[207]. IL10 deficiency accelerates diabetes by promoting neutrophil generation and activating $CD4^+$ T-cells in a mouse model of T1DM[208]. The anti-inflammatory action of IL10 is lower in whole blood cultures prepared from patients with T2DM, although the serum levels of IL10 are not significantly different, suggesting an IL10-hyporesponsive state in diabetes[209]. IL10 knockout intensified kidney inflammation and fibrosis[210]. Some polymorphisms of the IL10 promoter have a protective effect on the risk of DKD in T2DM[211]. IL10 also exhibits multiple renoprotective effects after diabetic myocardial infarction: it reduces acute renal inflammation, upregulates heme clearance, attenuates fibrosis, and reduces proteinuria. IL10 reduces the production of ROS in proximal tubule cells and collagen synthesis in fibroblasts[212].

Identified based on its similarities to IL6, IL11 possesses anti-inflammatory activity. It is a proposed therapeutic agent for treating chronic inflammatory diseases such as Crohn's disease and rheumatoid arthritis. However, in the kidneys, the effect of this cytokine is unusual. IL11 is upregulated by TGF-β and required for its profibrotic effects. Produced initially by tubular cells of a damaged kidney, it stimulates EMT in an autocrine manner. Neutralizing IL11 significantly reduces the extent of fibrosis, inflammation, and tubular damage. Anti-IL11 promotes kidney regeneration and reverses EMT and renal dysfunction[213,214]. These studies suggest IL11 signaling as a therapeutic target for DKD; however, one must also recognize how this signaling affects other tissues. For example, IL11 levels detected in gingival crevicular fluid decrease progressively with decreasing glycemic control and increasing periodontal disease in patients with T2DM[215].

IL13 regulates gluconeogenesis in hepatocytes via STAT3; mice lacking IL13 develop hyperglycemia and insulin resistance, implicating IL13 in the development of diabetes[216]. Several studies show that serum levels of anti-inflammatory cytokines increase significantly in DKD patients and are positively correlated with DKD severity and risk of cardiovascular events but may not correlate with markers of inflammation[217-219]. Several explanations might explain such confusing results. Cytokines, like IL6 and IL4, can have pro- or anti-inflammatory effects depending on the context. Anti-inflammatory cytokines might be unable to balance the overwhelmingly pro-inflammatory state. Our lack of a better understanding of these cytokines in the context of DKD warrants deeper, well-designed studies.

Table 1. Potential inflammation-related biomarkers of DKD

Biomarker	Relevant findings	References
TNF-α	Serum TNF-α increases in DKD patients with increasing albuminuria DKD treatment suppresses urinary TNF-α	[186,234]
TNF-α receptors	Serum TNFR1 and TNFR2 levels predict renal functional decline in patients with T1DM and T2DM	[235-237]
MCP1/CCL2	Urinary MCP1/CCL2 levels correlate with albuminuria and may or may not predict eGFR decline	[237-239]
SAA	SAA increases in DKD patients and correlates with disease progression	[35]
IL6	Urinary IL6 levels indicate DKD severity Serum IL6 levels can predict atherosclerosis in DKD	[190]

TNF: Tumor necrosis factor; DKD: diabetic kidney disease; MCP: monocyte chemoattractant protein; CCL: chemokine (CC motif) ligand; SAA: serum amyloid A; IL: interleukin.

Suppressors of cytokine signaling

SOCS is a family of eight intracellular, cytokine-inducible proteins that can inhibit JAK/STAT signaling. Diabetic conditions induce SOCS in podocytes, mesangial, tubular, and inflammatory cells. SOCS inhibits high-glucose-induced JAK/STAT signaling in mesangial and tubular cells and normalizes creatinine clearance, UAE, and weight loss in diabetic rats mediated by diminishing inflammation[220].

Pro-resolving mediators

An unresolved acute inflammation converts to pathogenetic chronic inflammation. A distinct coordinated program to resolve inflammation commences soon after an inflammatory response begins. Broadly, pro-resolving mechanisms include an increase in phagocytosis, efferocytosis, and cytotoxic cell killing, wound healing, macrophage M2 polarization, Treg response, and a reduction in NFκB signaling, Th1, Th17 cell responses, pro-inflammatory cytokine production, platelet aggregation, inflammasome formation[221,222]. Eicosanoids (lipid-based signaling molecules) are critical in initiating and resolving inflammation. As inflammation progresses, eicosanoids switch from initial pro-inflammatory lipid mediators like prostaglandins and leukotrienes to pro-resolving lipid mediators like lipoxins, resolvins, and protectins. Higher lipoxin levels are associated with a lower risk of developing T2DM[223]. Lipoxin treatment reduced albuminuria, mesangial expansion, and collagen deposition and diminished established kidney disease, with evidence of preserved kidney function in a mouse model of DKD[224]. The lesser studied ω-3 fatty acid-derived mediators, resolvins, protectins, and maresins, also preserve kidney function and reduce inflammatory mediators in various models of kidney injury[225-228].

Pro-resolving mediators have emerged as therapeutic targets in numerous inflammatory diseases. The diabetic milieu with a relentless presence of pro-inflammatory inducers might explain the inefficient resolution of chronic low-grade inflammation. Pro-resolving mediator therapy holds promise for managing and even reversing DKD[222,229,230].

POSSIBILITIES

Comprehending the inflammatory processes associated with DKD will help detect it early and develop effective therapies to halt its progression and perhaps even reverse it. Therefore, mediators of inflammation implicated in the onset and progression of DKD are under study as diagnostic and prognostic biomarkers and potential therapeutic targets[18,76,96,184,231,232].

Biomarkers

The gold-standard biomarkers for identifying and classifying DKD are albuminuria and eGFR, focusing on kidney function. Pathogenic signaling and minor structural changes precede functional decline, which

Table 2. The drugs comprising the current standard of care for DKD have anti-inflammatory effects

Class of drugs	Mechanism of action	Anti-inflammatory effects	Renal effects	Adverse effects	References
ACE inhibitors	Inhibit conversion of angiotensin I to angiotensin II	Increase expression of TNF-α, IL6, CCL2/MCP1, and NFκB in glomeruli and tubular cells	Decreases hyperfiltration and albuminuria, decreases BP	Cough, angioedema, hyperkalemia	[240]
Angiotensin receptor blockers	Inhibit angiotensin effects by blocking the angiotensin II type 1 receptor	Same as ACE inhibitors	Decreases albuminuria, renoprotective, decreases BP	Hyperkalemia	[240]
Metformin	Enhances AMP kinase activity	Regulates tenascin C and TLR4/NFκB signaling	Slows the progression of vascular complications of DM, including DKD	Lactic acidosis in advanced DKD	[241]
SGLT2 inhibitors	Inhibit SGLT2 in proximal tubules	Reduce cellular stressors and direct anti-inflammatory effects	Decreases plasma glucose levels, diuresis, natriuresis, reduces BP, lowers proteinuria, renoprotective	Urinary infections, ketoacidosis	[77,242-247]
GLP1 receptor agonists	Stimulate GLP1 receptors	Reduce TNF levels	Reduces proteinuria, slows the progression of CKD, Induces weight loss	Nausea, vomiting, ketoacidosis, pancreatitis, medullary thyroid cancer	[77,161,248, 249]
Finerenone	Non-steroidal selective aldosterone receptor antagonist	Reduce cytokine-mediated oxidative stress and immune cell infiltration	Renoprotective, mild diuresis, anti-hypertensive, reduces albuminuria and slows GFR decline	Hyperkalemia, worsening of kidney function in advanced CKD	[96,250-252]

ACE: Angiotensin-converting enzyme; TNF: tumor necrosis factor; IL: interleukin; CCL: CC motif chemokine ligand; MCP: monocyte chemoattractant protein; NFκB: nuclear factor kappa B; BP: blood pressure; AMP: adenosine monophosphate; TLR: toll-like receptor; DM: diabetes mellitus; DKD: diabetic kidney disease; SGLT: sodium-glucose co-transporter; GLP: Glucagon-like peptide; CKD: chronic kidney disease; GFR: glomerular filtration rate.

portrays the unmet need for novel diagnostic biomarkers[18,76,157]. Using machine learning algorithms on human transcriptomic data and mouse experiments, Zhong *et al.* identified DKD diagnostic markers related to oxidative stress and inflammation: tenascin C, peroxidasin, tissue inhibitor metalloproteinases 1, and tropomyosin[233]. Further comprehensive studies are required to test each protein for its potential. Table 1 summarizes some promising inflammation-related candidates.

Therapy

The drugs used for diabetes and DKD management have anti-inflammatory properties [Table 2], which might partly explain their renoprotective effects[77,96,161,240-252]. Potential anti-inflammatory therapeutic strategies for DKD are in various stages of development. STAT3 inhibitors - nifuroxazide and S3I-201 - have shown promise in animal models[253,254]. STAT3-inhibitor Stattic ameliorates kidney injury in mouse models of Alport syndrome and lupus nephritis but remains to be tested for DKD[255,256]. Table 3 summarizes anti-inflammatory drugs for DKD therapy backed by clinical evidence. Phosphodiesterase-inhibitor pentoxifylline (FDA-approved for intermittent claudication) reduces eGFR decline, albuminuria, and urinary TNF-α in type 2 DKD[234]. Even if some of these get the final FDA approval, they will contribute significantly toward achieving improved cardio-renal-metabolic health of patients with DKD.

Table 3. Potential anti-inflammatory drugs for DKD therapy

Name	Mechanism of action	Renal effects	Status	References
Bardoxolone	Nrf-2 inducer (NFκB inhibitor)	Improves GFR	Phase 3	[257-263]
Pirfenidone	TGF-β inhibitor	Increases GFR	Phase 2	[264]
Baricitinib	JAK1/JAK2 inhibitor	Reduces proteinuria	Phase 2	[110]
PF-04634817	CCR2/5 antagonist	Modest reduction of proteinuria	Phase 2	[265]
CCX140-B	CCR2 inhibitor	Reduces proteinuria	Phase 2	[266]
ASP8232	VCAM1 inhibitor	Reduces albuminuria	Phase 2	[267]

Nrf: Nuclear factor erythroid 2-related factor; GFR: glomerular filtration rate; TGF: transforming growth factor; JAK: Janus kinase; CCR: CC motif chemokine receptor; VCAM: vascular cell adhesion molecule.

CONCLUSION

While DKD has been traditionally viewed as a non-inflammatory microvascular disease, it is now evident that inflammation plays an integral part in its onset and progression. Chronic presence of non-infectious factors continuously induces PRRs in immune and kidney cells, activating inflammatory pathways, causing immune cell infiltration, and progressive damage to renal function and architecture. The pathogenesis of DKD is complex and heterogeneous. The patients with DKD are also a heterogeneous population, and some groups within them will benefit from treatment targeting inflammation more than others. As we begin to actualize early biomarkers and rely on more than the current markers of kidney function, we can detect DKD earlier and potentially arrest the progression.

DECLARATIONS

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Authors' contributions

Contributed substantially to developing the manuscript with literature search, writing, and revisions: Chatterjee A, Prabhakar S

Contributed to several sections and figures which were later reviewed by the other authors: Tumarin J

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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