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Research Progress on Inflammatory Mediators Involved in the Micro-Inflammatory State of Diabetic Kidney Disease

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Abstract

Diabetic Kidney Disease (DKD) , a prevalent and severe chronic complication of diabetes, is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide. The pathophysiology of DKD is multifactorial, involving dysregulated glycolipid metabolism, hemodynamic abnormalities, renin-angiotensin system (RAS) overactivation, inflammation, autophagy impairment, oxidative stress, mitochondrial dysfunction, and genetic/epigenetic dysregulation. Emerging evidence highlights inflammation as a central driver of DKD progression. This review comprehensively examines the inflammatory mechanisms underlying DKD and explores novel anti-inflammatory therapeutic targets, which may slow disease progression, reduce mortality, and open new avenues for DKD treatment.

Keywords: Diabetic kidney disease; micro-inflammation; inflammatory mediators; cytokines; therapeutic targets

Introduction

Diabetic Kidney Disease (DKD), a major microvascular complication of both type 1 and type 2 diabetes, is characterized by renal dysfunction due to chronic hyperglycemia [1, 2]. Currently, DKD has surpassed primary glomerulonephritis as the leading cause of CKD and ESRD globally and is the strongest predictor of mortality in diabetic patients. According to the United States Renal Data System (USRDS) , the overall mortality rate in the ESRD population is 13.59%, with DKD patients facing an annual mortality rate of approximately 20%. The pathophysiological mechanisms of DKD are multifactorial, with renal injury marked by mononuclear cell and macrophage infiltration. The accumulation of these immune cells correlates with the histological severity of DKD [3, 4]. During kidney injury, M1 macrophages secrete proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, matrix metalloproteinase-9 (MMP-9) and tumor necrosis factor-α (TNF-α) [5]. These mediators, acting via autocrine and paracrine pathways, serve as critical immune effectors, with IL-1, IL-6, IL-18 and TNF-α playing key regulatory roles in inflammation [6]. Consequently, targeting inflammatory pathways represents a promising therapeutic strategy for DKD. This review examines the roles of inflammatory mediators in DKD and explores their potential as therapeutic targets.

Table 1: Key inflammatory mediators in DKD pathogenesis

Mediator	Cellular Source	Biological Actions	Pathological Impact on DKD
TNF-α	Macrophages, podocytes	Activates NF-κB, induces chemokine secretion[7]	Glomerular hypertrophy, endothelial dysfunction
IL-1β	Inflammasome-activated macrophages[8]	Promotes NLRP3 activation, impairs autophagy	Tubulointerstitial fibrosis, oxidative stress[5]
IL-6	Macrophages, Tubular epithelial cells[8]	Stimulates B-cell differentiation, neutrophil recruitment	Podocyte EMT, albuminuria[7]
MCP-1/CCL2	Proximal tubule cells	Recruits monocytes/macrophages	Interstitial inflammation, fibrosis[9]
MMP-9	Mesangial cells[8]	ECM remodeling imbalance	Glomerular basement membrane thickening[10]
hs-CRP	Hepatocyte（pro-inflammatory cytokines induced）[11]	Activates TGF-β/Smad3 signaling	Renal fibrosis, endothelial injury[12]

Inflammatory Pathway-Related Molecules and DKD

Chronic inflammation is pivotal in DKD progression. Renal biopsies from DKD patients show elevated expression of inflammatory cytokines, chemokines and growth factors [13]. Persistent hyperglycemia promotes advanced glycation end product (AGE) accumulation, activating pathways such as protein kinase C (PKC), hexosamine and polyol flux, which drive microinflammation and upregulate inflammatory mediators [2]. These changes alter cytokine and chemokine levels [14, 15], triggering renal inflammation, glomerular hypertrophy, and endothelial damage [16, 17], ultimately leading to glomerulosclerosis, tubular atrophy, and renal function decline [18, 19]. Below, we discuss key inflammatory mediators in DKD.

Tumor Necrosis Factor-α (TNF-α)

In early diabetes, TNF-α released by activated macrophages exhibits increased expression in the glomerular and tubular cells.

Upregulated TNF-α not only induces the infiltration of other cytokines and chemokines into the kidney but also actively contributes to DKD pathology, as supported by multiple studies [4, 7]. Specifically, Yang et al. demonstrated that the NF-κB/TNF-α signaling pathway in activated macrophages exacerbates DKD progression [20]. Additionally, Xiang et al. confirmed elevated TNF-α expression in DKD rat models [17]. Niewczas et al. constructed the Kidney Risk Inflammatory Signature (KRIS), a protein panel containing 17 TNF receptor superfamily members, which predicts the 10-year risk of ESRD in diabetic patients, providing a valuable prognostic tool for DKD [21].

Interleukin-1β (IL-1))

IL-1β is a potent pro-inflammatory cytokine that mediates the expression of genes involved in secondary inflammation and is essential for host defense mechanisms [22]. It stimulates NLRP3 inflammasome activation in macrophages, further amplifying IL-1β production and exacerbating tissue damage in chronic and acute kidney injury [16, 23]. Studies have shown that infiltrating macrophages release substantial IL-1β in DKD patients, increasing endothelial permeability via prostaglandin E and phospholipase A2, contributing to glomerular hyperfiltration [7, 22]. Additionally, hyperglycemia-induced Akt phosphorylation and AMPK inhibition impair autophagy, worsening oxidative stress and renal inflammation [24]. Han et al. verified that metformin reduces IL-1β expression via the AMPK-mitophagy pathway, alleviating renal oxidative stress and fibrosis in diabetic mice [25].

Interleukin-6 (IL-6)

IL-6, a multifunctional cytokine, promotes lymphocyte proliferation, B-cell differentiation [26], and neutrophil infiltration, contributing to glomerular basement membrane thickening, podocyte hypertrophy, and albuminuria [7]. Studies confirm elevated IL-6 mRNA expression in renal cells of diabetic patients, correlating with DKD histopathological changes [3].In addition, Shikano et al. found that serum IL-6 levels are elevated in DKD patients and positively associated with disease progression [27].

Interleukin-16 (IL-16)

IL-16, an immunoregulating chemokine, signals through $CD4^+$ T cells, monocytes, macrophages and dendrital cells, enhancing antibacterial responses and inhibiting HIV replication [28]. An et al. observed increased IL-16 levels in a non-human primates DKD model, suggesting its involvement in DKD pathogenesis [7, 29].

Interleukin-18 (IL-18)

IL-18, expressed in kidney tissue, induces apoptosis, interferon-γ release, and adhesion molecule expression [7, 22]. In DKD patients, chronic hyperglycemia elevates IL-18 levels, which correlate with disease progression and albuminuria [22]. Chen et al. found that AMPK pathway activation reduces IL-18 levels in DKD models [30].

Monocyte Chemoattractant Protein-1 (MCP-1/CCL2)

MCP-1, also known as CC chemofactor ligand 2 (CCL2), highly expressed in renal tubular epithelial cells, promotes immune cell recruitment and inflammation [5, 31]. In type 2 diabetes, oxidative stress upregulates MCP-1, contributing to kidney damage [32, 33]. Tian et al. identified urinary MCP-1 as an independent predictor of CKD progression in DKD [34]. Sugahara et al. reported a 24-fold increase in renal MCP-1 mRNA in obese diabetic mice [35], while clinical studies link elevated plasma MCP-1 to DKD progression [9]. By reducing creatinine and proteinuria, lowering MMP-9 can effectively slow down the progression of DKD [36].

Matrite metalloproteinase-9 (MMP-9)

MMP-9 is a member of the matrix metalloproteinase family, which provides a steady state between the synthesis and degradation of extracellular matrix to maintain the structural and functional integrity of the glomerular [37, 38]. In DKD models, urinary and serum MMP-9 levels rise before microalbuminuria, correlating with declining GFR [10, 36], suggesting its potential as an early DKD biomarker.

High-Sensitivity C-Reactive Protein (hs-CRP)

hs-CRP, a nonspecific inflammation marker, increases in DKD patients, reflecting chronic low-grade inflammation [39, 40]. Elevated CRP correlates with reduced GFR and predicts kidney mortality [41, 42]. CRP exacerbates renal fibrosis via TGF-β/Smad3 signaling, directly promoting DKD progression [12, 43].

Anti-Inflammatory Therapy for DKD

Inflammatory cytokines (IL-6, TNF-α, IL-1β) are significantly upregulated in diabetic kidney disease (DKD), contributing to inflammatory responses and exacerbating renal dysfunction. Their levels closely correlate with disease progression. Antagonists targeting these cytokines have emerged as a novel therapeutic strategy for DKD (Table 2).

Table 2: Summary of Anti-Inflammatory Therapies for DKD

Drug Class	Representative Agents	Anti-Inflammatory Mechanism	Clinical Evidence
SGLT2 Inhibitors	Canagliflozin, Dapagliflozin	Suppress TXNIP/NLRP3 pathway, reducing IL-1β/IL-18 releases; decrease macrophage infiltration	35% reduction in UACR, delayed eGFR decline (CREDENCE trial) [44, 45]
GLP-1 RAs	Semaglutide, Dulaglutide, Exenatide	Inhibit NF-κB pathway, reduce M1 macrophage polarization, upregulate PPARα anti-inflammatory pathway	18% lower risk of kidney events (LEADER trial) [46]
Nonsteroidal MRA	Finerenone	Block MR-mediated release of TNF-α/IL-6; suppress fibrosis	34% reduced ESRD risk in Asian subgroup (FIDELITY analysis) [44]
JAK Inhibitors	Baricitinib	Inhibit JAK1/2-STAT3 pathway, reducing pro-inflammatory cytokines (IL-6/IL-17)	Phase II trial: 40% reduction in proteinuria, attenuated inflammation [47, 48]
Complement Inhibitors	NOX-D21 (C3aR antagonist)	Inhibit IκBα phosphorylation and TGF-β/Smad3 signaling	Reduced cytokine release, improved renal injury [49]
NLRP3 Inhibitors	MCC950、M920	Suppress caspase-1 activity, inhibit p38 MAPK and ERK1/2 pathways, reduce ROS generation	Decreased IL-1β expression, attenuated tubulointerstitial injury [50, 51]（
CCR2 Antagonists	CCX140-B、NOX-E36	Mitigate insulin resistance, reduce macrophage infiltration, lower albuminuria	Sustained improvements in proteinuria and glycemia in T2DM [52]
PKC Inhibitors	Ruboxistaurin (PKCβ inhibitor)	Normalize hyperglycemia-induced oxidative stress; inhibit TGF-β1/Smad pathway	Reduced renal inflammation, renoprotective effects [53]

TLR4 Antagonists	CRX-526	Inhibit NF-κB activation and TGF-β expression	Attenuated proteinuria, macrophage infiltration, and tubulointerstitial fibrosis [54]
Adhesion Molecule Inhibitors	ASP8232 (VAP-1 inhibitor)	Suppress MAP/NF-κB inflammatory signaling	Phase II trial: significantly reduced proteinuria and slowed renal decline [55]
Anti-IL-1β mAb	gevokizumab	Restore insulin production/action	Improved glycemia and reduced inflammation in T2DM [56, 57]
Nonspecific PDE Inhibitors	Pentoxifylline	Activate protein kinase A (PKA)	Suppressed production of IL-6, TNF-α, etc.[58]
Endothelin Receptor Antagonists	Atrasentan (ETA antagonist)	Promote vasoconstriction, inflammation, fibrosis, and cell proliferation	35% reduction in proteinuria in T2DM patients [44]

Note: SGLT2, Sodium-glucose cotransporter-2; NLRP3, NLR family pyrin domain containing 3 inflammasome; GPT1, Glutamic-Pyruvic Transaminase 1; NF-κB, nuclear factor-kappa B; PPARα, Peroxisome Proliferator-Activated Receptor Alpha; JAK1-2/STAT3, Janus Kinase 2/Signal Transducer and Activator of Transcription 3; IκBα, Inhibitor of kappa B alpha; TGF-β/Smad, TGF-β/Smad signaling pathway; caspase-1, cysteine-aspartic protease 1; P38 MAPK, p38 mitogen-activated protein kinase; ERK1/2, Extracellular Signal-Regulated Kinase 1/2; ROS, Reactive Oxygen Species; CCR2, C-C Chemokine Receptor Type 2; PKC, Protein Kinase C; TGF-β1, Transforming Growth Factor-beta 1; TLR4, Toll-like receptor 4; MAP, Mitogen-Activated Protein; VAP-1,Vascular Adhesion Protein-1;ETA,Endothelin Receptor Type A.

Limitations of current Anti-Inflammatory strategies

Targeting inflammatory pathways has shown potential in the treatment of diabetic kidney disease (DKD), but it still faces multiple challenges. First, the complex pathogenesis of chronic inflammation has led to insufficient research on therapeutic targets: although cytokine-targeted therapy is widely used in autoimmune diseases, similar research on DKD is still in the exploratory stage [59]. New agents currently in clinical trials include NF-κB modulators (bindarit, NCT01109212), CCR2 selective inhibitor CCX140-B (NCT01447147), CCR2/5 dual antagonist PF-04634817 (NCT01712061) and Spiegelmer emapticap pegol (NOX-E36, NCT01547897) et al [60, 61].Second, existing drugs have significant safety hazards. Clinical studies have shown that bispecific antibodies (such as bimekizumab and sonelokimab) have a risk of systemic immunosuppression in the treatment of autoimmune diseases such as ankylosing spondylitis and psoriasis [62]. The phase Ⅱ clinical trial of JAK1/JAK2 inhibitor baricitinib (NCT01683409) can reduce albuminuria and inflammatory markers (CXCL10, CCL2, TNF-R1/2, ICAM-1), but it is accompanied by adverse reactions such as anemia and liver function damage [63]. In addition, most new drugs lack long-term safety verification, and the development of Bardoxolone was terminated due to the risk of heart failure associated with fluid retention in the BEACON study [64].

Conclusion

Currently, no definitive treatment halts DKD progression. Growing evidence underscores inflammation as a key driver of DKD, making anti-inflammatory therapies a promising strategy. This review highlights critical inflammatory mediators in DKD and their therapeutic potential. However, further mechanistic studies are needed to develop targeted therapies and preventive strategies, reducing the global burden of DKD.

CRediT Authorship Contribution Statement

Shasha Wang: Conceptualization, Writing – original draft. Mingjing Li: Writing – review & editing. Haidong Shan: Writing – review & editing. Yanfang Lu: Writing – review & editing. Huixia Cao: Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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