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REVIEW

Innovative Insights into Interleukin-Mediated Macrophage Polarization: Metabolic Reprogramming and Inflammatory Pathway Crosstalk in Chronic Kidney Disease and Therapeutic Implications—A Narrative Review

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Objective: To clarify the molecular mechanisms of interleukin-macrophage polarization axis in reshaping renal inflammatory microenvironment and driving chronic kidney disease (CKD) progression, and explore targeted therapeutic potential.

Methods: We systematically searched the PubMed and Embase databases for published studies from January 2015 to March 2026. The search terms used were "chronic kidney disease" or "CKD", "interleukin" or "IL" or "leukocyte protein network", "macrophages" and "inflammation". A total of 186 peer-reviewed studies based on human and animal models were included, with all non-eligible articles excluded in the screening process.

Results: Pro-inflammatory interleukins (IL-1β/IL-6/IL-17) orchestrate M1 polarization via multi-pathway crosstalk: IL-1β activates NLRP3 inflammasome to promote IL-18 release, IL-6 binds gp130 to trigger STAT3, and IL-17 activates NF-κB/MAPK, all upregulating glycolytic enzymes (HK2/PFKFB3) and M1 markers (iNOS/CD86). Activated M1 macrophages secrete TNF-α/IL-1β/IL-6, forming an autocrine loop to amplify renal parenchymal injury and monocyte recruitment. Anti-inflammatory interleukins (IL-10/IL-22) induce protective M2 polarization: IL-4 activates STAT6 to upregulate CD206/Arg1, IL-10 inhibits NF-κB, and IL-22 modulates AMPK-mediated mitophagy. However, CKD-induced M2 pathological deviation (elevated TGF-β/CTGF, reduced IL-10) converts reparative functions to profibrotic effects, accelerating glomerulosclerosis. This polarization imbalance forms a vicious cycle with interleukin dysregulation. Targeted interventions show efficacy: tocilizumab (anti-IL-6R) reduces M1 infiltration and urinary albumin; paeoniflorin upregulates IL-10 via KLF4 to induce M2; SGLT2 inhibitors enhance IL-22/AMPK signaling; astragaloside IV promotes IL-4/PPARγ to stabilize M2 polarization, all alleviating inflammation and fibrosis.

Conclusion: The interleukin-macrophage polarization axis, regulated by inflammatory pathways and metabolic reprogramming, is a core CKD therapeutic target, supporting multi-target precision interventions.

Keywords: chronic kidney disease, interleukin, macrophage polarization, inflammatory pathway, renal fibrosis, metabolic reprogramming

Introduction

Chronic kidney disease (CKD) has become a major global public health problem. The incidence of chronic kidney disease worldwide increased from 7.8 million in 1990 to 18.99 million in 2019.[1,2] Patients with end-stage renal disease (ESRD) depend on dialysis or renal transplantation to sustain life, and this situation places a heavy burden on both

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society and families.[3] Current clinical treatments mainly focus on controlling risk factors including high blood pressure and blood glucose. Renin-angiotensin system inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors can delay the decline of renal function, but they cannot fundamentally block the core pathological process of renal inflammation and fibrosis. The application of immunosuppressive agents in autoimmune kidney diseases also has limitations such as non-specific targeting and elevated infection risk. Novel precision therapeutic strategies that target the core pathology of CKD are thus urgently needed in clinical settings.[4,5]

CKD is essentially a vicious cycle of inflammation and fibrosis initiated by renal injury. Initial injurious factors such as diabetes mellitus, hypertension and autoimmune responses can induce resident renal cells including renal tubular epithelial cells and glomerular mesangial cells to release damage-associated molecular patterns.[6] These factors also recruit peripheral blood monocytes to infiltrate the kidney and differentiate into macrophages.[7,8] Under normal physiological conditions, macrophages can eliminate inflammation and facilitate tissue repair through phenotypic switching. Macrophages are broadly categorized into two main functional phenotypes: classically activated M1 macrophages and alternatively activated M2 macrophages. M1 macrophages exert pro-inflammatory effects, secreting cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) to initiate and amplify inflammatory responses. In contrast, M2 macrophages primarily mediate anti-inflammatory and tissue-repairing functions, producing IL-4, IL-10, and transforming growth factor-β (TGF-β) to resolve inflammation and promote tissue remodeling.[9,10] However, macrophages show imbalanced polarization in the pathological microenvironment of CKD. The pro-inflammatory M1 phenotype is excessively activated and continuously secretes pro-inflammatory factors to aggravate renal parenchymal damage. The M2 phenotype undergoes pathological deviation with weakened reparative function and enhanced pro-fibrotic effect, which ultimately promotes glomerulosclerosis and tubulointerstitial fibrosis.[11,12] This polarization imbalance forms a bidirectionally regulated pathological loop with renal inflammation and serves as the core driving force for the progression of CKD.[13,14]

Interleukins represent a core family of cytokines that regulate the activation and differentiation of immune cells. Dysregulated expression of interleukins in the renal microenvironment of CKD acts as a key inducer of aberrant macrophage polarization. Pro-inflammatory interleukins such as IL-1β, IL-6 and IL-17 continuously promote macrophage polarization toward the M1 phenotype by activating downstream signaling pathways.[15,16] Anti-inflammatory interleukins including IL-4, IL-10 and IL-33 induce macrophages to convert into the protective M2 phenotype for the maintenance of immune homeostasis.[17] Recent studies have verified that interleukins are not simply pro-inflammatory or anti-inflammatory mediators. The regulation of macrophage polarization by interleukins shows dose dependence, cell specificity and disease stage specificity, and constructs a sophisticated hierarchical regulatory network.[18,19] Targeting this network to restore the balance of macrophage polarization allows intervention in the pathological process of CKD at the upstream inflammatory level. This approach exerts dual therapeutic effects of anti-inflammation and anti-fibrosis, and offers a novel target-oriented strategy for the treatment of CKD.[20,21]

Current interleukin-targeted therapies for CKD predominantly adopt single-agent strategies with suboptimal clinical performance. Monoclonal antibodies targeting pro-inflammatory interleukins, such as canakinumab (anti-IL-1β), have advanced to Phase II/III clinical trials for diabetic nephropathy and hyperuricemic nephropathy, demonstrating partial efficacy in reducing renal inflammation and proteinuria.[22,23] However, several single-target agents have failed in late-stage trials, mainly due to their inability to address the complex, multi-factorial pathogenesis of CKD, non-specific systemic side effects, and failure to modulate the intricate interleukin-macrophage polarization crosstalk. These limitations underscore the critical need for multi-target therapeutic strategies that synergistically regulate the interleukin network and restore balanced macrophage polarization.

Although the critical role of interleukin-mediated macrophage polarization in CKD has been widely documented, current studies still present several critical limitations. First, there is insufficient understanding of the heterogeneity in macrophage polarization and the corresponding interleukin expression profiles across different etiologies and stages of CKD. This insufficient understanding leads to a limited response rate to single-target therapeutic approaches. Second, the metabolic reprogramming mechanism that underlies the regulatory effect of interleukins on macrophage polarization has not been fully clarified. This knowledge gap restricts the development of combined metabolic intervention strategies. Third, the molecular targets of natural products derived from traditional Chinese medicine (TCM) in regulating this axis

remain inadequately defined. This uncertainty hinders the standardization and clinical translation of such natural products. Fourth, the shortcomings of renal targeted delivery technologies make it difficult to avoid the systemic side effects caused by interleukin-targeted drugs. Based on the current research progress worldwide, this review systematically integrates the pathological mechanisms, intervention strategies and translational advances of interleukin-mediated macrophage polarization in CKD. It also dissects the controversies and challenges in this field and aims to provide a comprehensive theoretical framework for basic research and clinical translation in this direction.

Method

Search Strategy

This work adopts a systematic narrative literature review methodology—a rigorous approach that synthesizes, analyzes, and interprets existing peer-reviewed evidence without conducting original empirical research. The review strictly adheres to the PRISMA guidelines for literature search, screening, and data synthesis, with predefined inclusion/exclusion criteria and standardized data extraction procedures, ensuring methodological clarity, reproducibility, and objectivity. We systematically searched the PubMed and Embase databases for peer-reviewed original research and clinical studies published from January 2015 to March 2026. This timeframe was selected to capture the most recent cutting-edge advances in interleukin-mediated macrophage polarization and CKD research, ensuring the inclusion of state-of-the-art mechanistic insights and translational findings. The search keywords were: ("chronic kidney" or "CKD"), ("interleukin" or "IL" or "Interleukin Network"), ("macrophage polarization" or "macrophage"), and ("inflammation" or "fibrosis").

Study Selection and Data Extraction

Prior to the full-text assessment of shortlisted articles, EndNote software was used to screen references relevant to the research topic. Initial screening was implemented through the native search tools of each database, and 562 relevant articles were identified after excluding 385 duplicate records. Afterwards, 186 eligible full-text original research papers were included for analysis after excluding 85 articles without full-text abstracts, 145 studies irrelevant to CKD and IL, and 146 review articles or meta-analyses. A flowchart of the entire literature search and selection process is provided in Supplementary Figure 1. Given overlapping content in existing relevant research, we selected representative literature. Data extraction was first conducted by the first author and then cross-checked by co-authors, and this dual verification ensured the integrity and reliability of the collected data, laying a solid foundation for subsequent efficacy analysis and mechanistic exploration.

General Overview of Interleukin-Mediated Inflammatory Network Regulation in CKD

Biological Characteristics of Interleukins and Their Secretory Regulation in CKD

Interleukins are a group of small molecular polypeptides mainly secreted by immune cells. According to their structures and functions, interleukins can be classified into multiple families. These families include the IL-1 family, IL-2 family which is also called the γc chain family, IL-6 family and IL-10 family. Their biological effects depend on the binding of specific receptors and the activation of downstream signaling pathways.[24] In normal renal tissues, interleukins are expressed at low levels.[25] They mainly participate in renal immune surveillance and the maintenance of tissue homeostasis. In the pathological state of CKD, factors in the renal microenvironment such as high glucose, uremic toxins and oxidative stress can induce secretory reprogramming in resident renal cells and infiltrating immune cells.[26,27]

Renal tubular epithelial cells represent an important source of interleukin secretion in CKD. These cells can secrete pro-inflammatory factors including IL-1β, IL-34 and IL-6 after injury, and then recruit and activate macrophages.[28,29] Glomerular mesangial cells secrete IL-6 via the TLR4 pathway under high glucose stimulation, which further amplifies the renal inflammatory response.[30] Infiltrating macrophages also secrete large amounts of interleukins through autocrine and paracrine manners to trigger a cascade reaction. M1 macrophages are responsible for the secretion of IL-1β, IL-6 and IL-18, while M2 macrophages secrete IL-10, TGF-β and IL-33.[31,32] In addition, the regulatory role of the gut-kidney axis has received increasing attention. Metabolites of the gut microbiota such as trimethylamine N-oxide (TMAO) can induce

renal macrophages to secrete IL-6 through the blood circulation and aggravate the inflammatory response.[33,34] Such multicellular-derived regulation of interleukin secretion contributes to the formation of a unique inflammatory cytokine network in CKD.[35]

Core Features of Inflammatory Injury in CKD and the Pivotal Role of Macrophage Polarization

Inflammatory injury in CKD is characterized by chronicity, low grade and persistence, which is clearly different from the explosive inflammation in acute kidney injury.[36] The inflammatory microenvironment is formed by pro-inflammatory cytokines, infiltrating immune cells and extracellular matrix components. Macrophages are the most numerous and functionally critical immune cells within this microenvironment.[14,37] Macrophages display high plasticity, and their polarization state is strictly controlled by signals derived from the local microenvironment. They are mainly divided into the classically activated M1 phenotype and the alternatively activated M2 phenotype. These two phenotypes are functionally antagonistic and work together to maintain renal immune homeostasis.[38,39]

Core markers of M1 macrophages include CD86 and inducible nitric oxide synthase (iNOS). M1 macrophages mainly secrete pro-inflammatory cytokines such as IL-1β, IL-6 and tumor necrosis factor-α (TNF-α). Excessive activation of these cells can induce necrosis of renal tubular epithelial cells and damage to glomerular capillaries, and further aggravate renal inflammatory infiltration.[4,40] M2 macrophages can be further divided into several subsets including M2a, M2b and M2c. The core markers of M2 macrophages are CD206 and arginase 1 (Arg-1).[41,42] Under normal conditions, M2 macrophages secrete factors such as IL-10 and TGF-β to participate in inflammation resolution and tissue repair. However, M2 macrophages undergo pathological deviation in the setting of CKD. Their reparative function is weakened, and the secreted TGF-β can induce the activation of fibroblasts to accelerate the progression of renal fibrosis.[12,43]

Macrophage polarization imbalance plays a critical role throughout the entire progression of CKD. Excessive activation of M1 macrophages triggers the renal inflammatory response at the early stage of the disease. Imbalanced M1/M2 polarization acts as the intermediate link connecting inflammation and fibrosis during the middle stage. Pathological M2 macrophages serve as the core driving force of renal fibrosis at the late stage of the disease.[14,44] Multiple clinical studies have verified that the infiltration level of M1 macrophages in renal tissues is positively correlated with the degree of renal function impairment in patients with CKD. The abnormally increased proportion of M2 macrophages in peripheral blood is closely related to the progression of renal fibrosis.[37,45]

Dual Roles of Interleukins in the Regulation of Inflammatory Networks in CKD

Interleukins exert complex dual roles in the inflammatory network of CKD (Table 1). This property is closely associated with the interleukin family type, expression level, target cell type and disease stage. The duality of pro-inflammatory interleukins is mainly reflected in the transition between physiological defense and pathological injury. IL-1β can activate macrophages to eliminate pathogens during acute infection.[46] However, its persistent high expression amplifies the inflammatory response through the NLRP3 inflammasome and aggravates renal injury in CKD.[20,47] IL-17 plays an important role in normal immune defense. Low-dose IL-17A can induce macrophage M2 polarization by activating the AMPK pathway, while high-dose IL-17A promotes M1 polarization. This dose-dependent effect reflects the complexity of its regulatory function.[18,48]

The dual role of anti-inflammatory interleukins is reflected in the contradiction between tissue repair and pro-fibrotic effects. IL-10 is a classic anti-inflammatory cytokine that can block macrophage M1 polarization by inhibiting the NF-κB pathway and alleviate renal inflammation.[48] However, excessive IL-10 can suppress the anti-fibrotic immune response of the body and indirectly promote renal fibrosis. Notably, a recent animal research report suggests that high expression of IL-10 is associated with worsening renal fibrosis, challenging the traditional anti fibrotic view of IL-10.[60] IL-33 induces macrophage M2 polarization through the ST2 receptor to exert anti-inflammatory effects.[31] Nevertheless, its overexpression can lead to abnormal macrophage function and aggravate graft injury in the setting of chronic renal transplant rejection.[55]

In addition, the synergistic and antagonistic interactions among interleukins further contribute to the formation of their dual regulatory network. IL-1β and IL-18 act synergistically to activate M1 polarization of macrophages and aggravate renal injury in diabetic nephropathy.[49] IL-6 and IL-10 antagonize each other to regulate the balance of

Table 1 Dual Role of Interleukin in the Regulation of CKD Inflammatory Network

Interleukin	Family	Model	Pro-Inflammatory/ Anti-Inflammatory	Signaling Pathway	Key Molecular Targets	Result	Reference
IL-1β	IL-1 Family	Gouty nephropathy mouse model; CKD patients; AKI-CKD model	Pro-inflammatory	NLRP3/NF-κB pathway	NLRP3 inflammasome, NF-κB p65, caspase-1	Activates NLRP3 to promote IL-1β maturation, induces M1 macrophage polarization, aggravates renal inflammation and fibrosis; inhibition alleviates renal injury	[20,29,49]
IL-6	IL-6 Family	Diabetic nephropathy model; Lupus nephritis model; CKD patients; Salt-sensitive hypertension model	Pro-inflammatory	JAK2/STAT3 pathway	STAT3, SOCS3, gp130	Activates STAT3 to drive M1 polarization, forms inflammatory positive feedback loop, accelerates renal injury and fibrosis	[26,40,50,51]
IL-10	IL-10 Family	Ischemic renal injury-CKD transition model; UUO model; AKI mouse model	Anti-inflammatory	STAT3 pathway	STAT3, CD206, Arg1	Activates STAT3 to induce M2c polarization, inhibits M1 activation, reduces renal interstitial inflammation and fibrosis; EV-encapsulated IL-10 enhances renal targeting effect	[21]
IL-11	IL-6 Family	CKD mouse model	Pro-inflammatory	STAT3/ERK1/2 pathway	IL-11Rα, metadherin	Mediates macrophage-tubular epithelial cell crosstalk, promotes M1 polarization and EMT/MMT, drives renal inflammation and fibrosis; neutralizing antibody improves renal pathology	[52]
IL-17	IL-17 Family	Lupus nephritis model; CKD mouse model; Diabetic nephropathy model	Dual (pro-inflammatory at high concentration; anti-inflammatory at low dose)	STAT3/NF-κB pathway	STAT3, NF-κB	High concentration promotes M1/M2a abnormal activation and amplifies inflammation; low dose inhibits STAT3 phosphorylation and upregulates anti-inflammatory proteins to improve diabetic nephropathy	[18, 53]
IL-33	IL-1 Family	UUO mouse model	Dual (anti-inflammatory at low concentration; pro-inflammatory at high concentration)	ST2/AKT/NF-κB pathway	ST2 receptor, ILC2s, NF-κB	Low concentration exerts anti-inflammatory and repair effects; high concentration activates NF-κB to aggravate M1 polarization and obstructive renal injury	[54]
IL-4	IL-2 Family	UUO model; Diabetic nephropathy model; AKI-CKD transition model	Dual (anti-inflammatory in physiology; pro-fibrotic in pathology)	JAK1/STAT6 pathway	STAT6, CD206, Arg1	Physiological concentration induces M2 polarization for repair; pathological high concentration promotes M2a pathological polarization and TGF-β1 secretion to exacerbate fibrosis	[55, 56]
IL-15	IL-2 Family	UUO mouse model; CKD model	Anti-inflammatory	AMPK pathway	AMPK, glycolysis-related genes	Regulates macrophage metabolic reprogramming, inhibits M1 polarization, reduces collagen synthesis and prevents renal fibrosis	[57]
IL-34	Other interleukins	CKD mouse model; Renal fibrosis model	Pro-inflammatory	YAP/Hippo pathway	YAP, integrin αvβ6	Secreted by tubular epithelial cells via αvβ6/YAP axis, promotes macrophage migration and pro-inflammatory differentiation, mediates renal inflammation	[28]

(*Continued*)

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Table 1 (Continued).

Interleukin	Family	Model	Pro-Inflammatory/ Anti-Inflammatory	Signaling Pathway	Key Molecular Targets	Result	Reference
IL-18	IL-1 Family	Gouty nephropathy model; AKI-CKD model	Pro-inflammatory	NLRP3 inflammasome pathway	NLRP3, TGF-β, TNF-α, IL-1β	Co-activated with IL-1β by NLRP3, promotes M1 polarization and inflammatory cascade, aggravates renal inflammatory injury	[49]
IL-27	IL-6 Family	UUO model; CKD model	Anti-inflammatory	STAT1/STAT3 pathway	STAT1, STAT3	Induces macrophage anti-inflammatory and anti-fibrotic phenotype, inhibits M1 polarization, upregulates IL-10 and CD206, alleviates renal inflammation and fibrosis	[58]
IL-35	Other interleukins	5/6 nephrectomy model; CKD model	Anti-inflammatory	STAT6 pathway	STAT6	Promotes M2 macrophage polarization, inhibits pro-inflammatory and pro-fibrotic factors, improves renal function and attenuates renal fibrosis	[59]

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney injury; UUO, unilateral ureteral obstruction.

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macrophage polarization, and their expression ratio can serve as an indicator for evaluating the inflammatory status of CKD.[50] Such dual roles indicate that interleukin-targeted therapy for CKD requires precise control of dosage, timing and disease classification to avoid the limitations of single-target therapy.[44]

Crosstalk Mechanisms Between Macrophage Polarization and Interleukin Networks in CKD

Polarization Characteristics and Functional Imbalance of Macrophages in CKD

Multiple factors in the pathological microenvironment of CKD collectively promote macrophage overactivation and development towards M1 phenotype, as shown in Figure 1. A high-glucose environment induces the differentiation of monocytes into M1 macrophages by activating the TLR4/NF-κB pathway, and this effect is particularly prominent in diabetic nephropathy.[30] Uric acid crystals, calcium oxalate crystals and other related substances can promote M1 polarization of macrophages and the release of IL-1β by activating the NLRP3 inflammasome.[50,61] These processes aggravate the progression of hyperuricemic nephropathy and CKD associated with renal calcification.[47,62] Uremic toxins such as indoxyl sulfate can induce macrophage pyroptosis by activating caspase-4/5. These toxins also promote M1 polarization at the same time, which leads to persistent inflammation.[63]

Excessively activated M1 macrophages aggravate the progression of CKD through multiple pathways. These cells secrete a large number of pro-inflammatory cytokines to form a cascade reaction.[64] IL-1β can induce renal tubular epithelial cells to secrete more pro-inflammatory cytokines, which forms a vicious cycle of injury and inflammation.[29] The released reactive oxygen species and nitrogen free radicals directly damage resident renal cells. This damage results

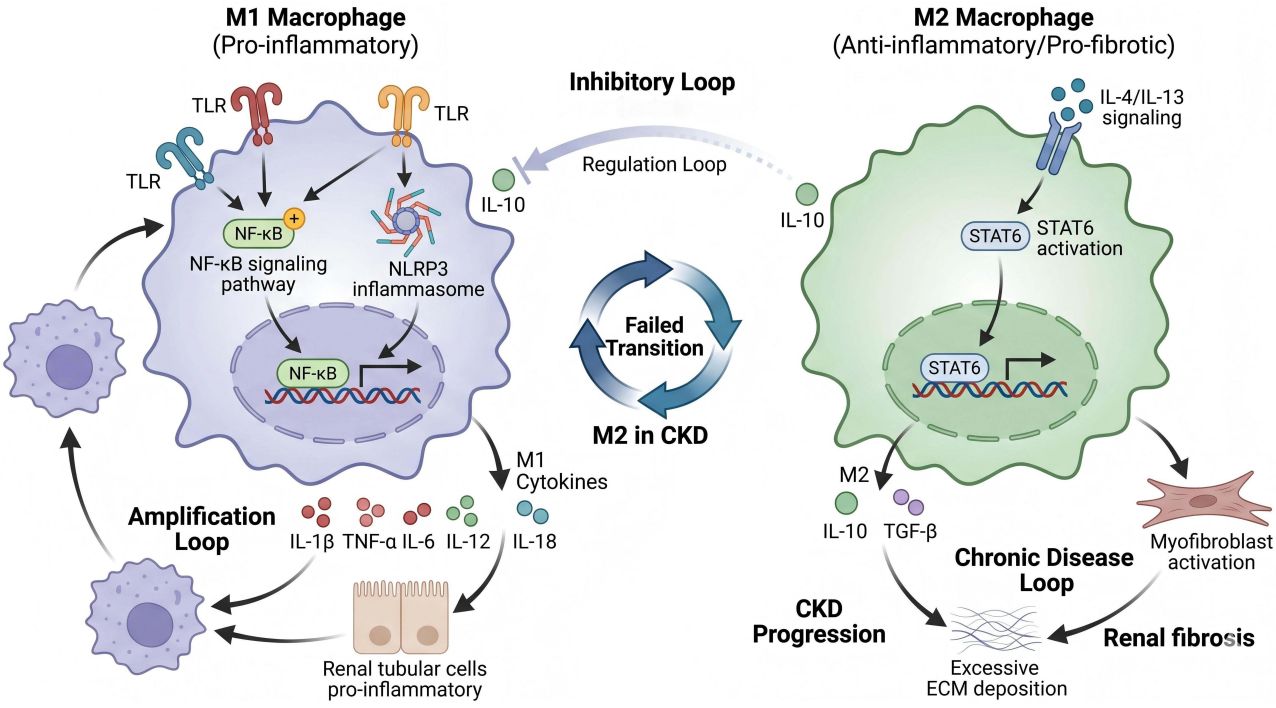

Figure 1 Crosstalk mechanisms between macrophage polarization and interleukin networks in CKD. M1 Macrophage (Pro-inflammatory) activation is triggered via Toll-like receptors (TLRs), leading to the activation of the NF-κB signaling pathway and the NLRP3 inflammasome. This induces the transcription and hypersecretion of M1 cytokines (eg, IL-1β, TNF-α, IL-6, IL-12, and IL-18). These cytokines initiate an Amplification Loop, promoting further M1 polarization and inducing pro-inflammatory responses in resident renal tubular cells, which in turn forms a vicious cycle of persistent renal injury and inflammation. M2 Macrophage (Anti-inflammatory/Pro-fibrotic) polarization is typically driven by IL-4/IL-13 signaling, which activates the STAT6 pathway. However, a Failed Transition occurs in the CKD microenvironment, leading to M2 pathological deviation. Because of this deviation, the physiological Inhibitory Loop (labeled "Regulation Loop")—where M2-derived IL-10 attempts to suppress M1 activation—fails due to disrupted polarization balance and reduced IL-10 efficacy. Consequently, these pathologically deviated M2 macrophages secrete excessive TGF-β, driving the Chronic Disease Loop. This fibrotic loop is characterized by myofibroblast activation and excessive extracellular matrix (ECM) deposition, ultimately accelerating Renal fibrosis and overall CKD Progression. Solid arrows (→) indicate directional process flow; dotted T-bars (—|) represent impaired inhibitory mechanisms; circular arrows denote self-reinforcing or failed transition loops; plus signs (+) indicate signaling activation.

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in the apoptosis of renal tubular epithelial cells and the proliferation of glomerular mesangial cells.[13] These cells activate T cells through antigen presentation and amplify the adaptive immune response. This process is particularly important in autoimmune kidney diseases such as lupus nephritis.[65] Clinical studies have found that the proportion of M1 macrophages in the peritoneal dialysate of patients with ESRD is significantly increased. The level of IL-6 secreted by these cells is closely related to dialysis-related complications.[66]

Traditionally, M2 macrophages have been regarded as reparative cells for renal injury. However, recent studies have demonstrated that M2 macrophages undergo pathological deviation in the setting of CKD. These cells exhibit weakened reparative function and enhanced pro-fibrotic effects, and thus act as the core driving force for renal fibrosis.[67,68]

This deviation is mainly manifested in three aspects. The expression of phenotypic markers is abnormal. The expression level of CD206 in M2 macrophages is elevated in CKD, but the anti-inflammatory and reparative function of Arg-1 is weakened.[69] In turn, this index is positively correlated with the secretion of TGF-β.[12] Functional polarization is in a state of imbalance. Pathological M2 macrophages secrete significantly increased levels of pro-fibrotic factors such as TGF-β and connective tissue growth factor. Meanwhile, the anti-inflammatory secretion of IL-10 is reduced.[43] Cell fate transformation takes place. Under the induction of TGF-β, M2 macrophages can undergo myofibroblast-like transformation.[70] These cells directly secrete extracellular matrix and accelerate the progression of renal fibrosis.[43,55]

Pathological deviation of M2 macrophages shows specificity in different etiologies of CKD. In obstructive nephropathy based on the UUO model, M2 macrophages induced by IL-33 mainly secrete pro-fibrotic factors and aggravate tubulointerstitial fibrosis.[54] In diabetic nephropathy, M2 macrophages induced by IL-4 promote the proliferation of glomerular mesangial cells and matrix deposition by activating the STAT6 pathway.[71] In chronic rejection after renal transplantation, M2 macrophages infiltrate into the graft interstitium. The TGF-β secreted by these cells acts as a key factor leading to graft fibrosis.[19]

This specificity indicates that pathological deviation of M2 macrophages is an important target for CKD fibrosis, instead of being simply anti-inflammatory and reparative cells.[44]

The disruption of macrophage polarization balance represents a core node in the transition from inflammation to fibrosis in CKD.[72] In the early stage of the disease, excessive activation of M1 macrophages initiates the inflammatory response. Renal injury remains reversible if the polarization balance can be restored at this stage. However, with disease progression, pro-inflammatory factors secreted by M1 macrophages continuously induce damage to resident renal cells. These factors also promote pathological deviation of M2 macrophages, which leads to the cascade effect of M1-mediated inflammation and M2-mediated fibrosis.[14]

The key mechanism underlying this cascade transition lies in the remodeling of the interleukin network. IL-6 secreted by M1 macrophages can activate the STAT3 pathway and induce the transformation of M2 macrophages into pro-fibrotic subsets.[14] IL-1β promotes the secretion of TGF-β from fibroblasts through activating these cells, which further drives the pathological deviation of M2 macrophages.[11] In the meantime, macrophages with imbalanced polarization establish crosstalk with resident renal cells. IL-34 secreted by renal tubular epithelial cells induces M1 polarization of macrophages, and TNF-α released by M1 macrophages aggravates the epithelial-mesenchymal transition of renal tubular epithelial cells.[28,73] Fibroblasts and pathological M2 macrophages form a positive feedback loop via TGF-β, which accelerates the deposition of extracellular matrix.[12,74] Ultimately, the disruption of such polarization balance results in persistent renal inflammation, progressive fibrosis and gradual decline of renal function.[13]

Hierarchical Regulation of the Interleukin Network on Macrophage Polarization

We have summarized the relevant studies on the regulation of macrophages by different interleukins to improve CKD inflammation in recent years, and the results are shown in Table 2. Pro-inflammatory interleukins form a hierarchical regulatory network by activating specific signaling pathways. This network continuously drives macrophages to polarize toward the M1 phenotype. IL-1β and IL-18 from the IL-1 family act as upstream initiators of macrophage M1 polarization.[75] The release of both cytokines depends on the activation of the NLRP3 inflammasome. IL-1β activates the NF-κB and MAPK pathways by binding to the IL-1R1 receptor.[76] It upregulates the expression of M1 markers such as iNOS and CD86 and inhibits the expression of M2 markers at the same time.[20,32] IL-18 enhances the pro-inflammatory function of macrophages by activating the STAT1 pathway. The synergistic interaction between IL-18

Table 2 Study on the Mechanism of Different Interleukins Regulating Macrophages to Improve CKD Inflammation

Interleukin	Family	Model	Signaling Pathway	Key Molecular Targets	Main Mechanism of Action	Result	Reference
IL-6	IL-6 Family	Diabetic nephropathy mouse model; Lupus nephritis model; CKD patients	JAK2/STAT3 pathway	STAT3, SOCS3	Activates STAT3 signaling to promote M1 macrophage polarization; forms IL-6/STAT3 positive feedback loop to amplify inflammation	Accelerates renal inflammation and fibrosis; anti-IL-6R antibody reduces M1 macrophage infiltration and improves renal function	[26,40,50,52]
IL-10	IL-10 Family	Ischemic renal injury-CKD transition model; UUO model; AKI mouse model	STAT3 pathway	STAT3, CD206, Arg1	Activates STAT3 to induce M2c macrophage polarization; inhibits M1 macrophage activation and pro-inflammatory factor secretion	Reduces renal interstitial inflammation and fibrosis; extracellular vesicle-encapsulated IL-10 enhances renal targeting and protective effect	[21]
IL-11	IL-6 Family	CKD mouse model	STAT3/ERK1/2 pathway	IL-11Rα, metadherin	Mediates macrophage-tubular epithelial cell crosstalk; promotes M1 macrophage polarization and MMT/EMT process	Drives renal inflammation and fibrosis; IL-11 neutralizing antibody breaks the pathological cycle and improves renal pathology	[52]
IL-17	IL-17 Family	Lupus nephritis model; CKD mouse model	STAT3/NF-κB pathway	STAT3, NF-κB	Synergizes with IL-6 to activate STAT3/NF-κB; promotes M1 macrophage polarization and M2a abnormal activation	Amplifies renal inflammation and glomerulosclerosis; anti-IL-17 antibody reduces abnormal macrophage polarization	[53]
IL-33	IL-1 Family	UUO mouse model; Kidney transplant model	ST2/AKT/NF-κB pathway	ST2 receptor, ILC2s	Dual-directional regulation: early low-concentration exerts anti-inflammatory effect; high-concentration activates NF-κB to aggravate M1 macrophage activation	Promotes obstructive renal injury and fibrosis via macrophage polarization; regulates graft macrophage to alleviate chronic rejection	[19,54]
IL-4	IL-2 Family	UUO model; Diabetic nephropathy model; AKI-CKD transition model	JAK1/STAT6 pathway	STAT6, CD206, Arg1	Activates STAT6 to induce M2a macrophage pathological polarization	Induces abnormal M2 macrophage polarization to exacerbate fibrosis; CD11b deficiency inhibits IL-4/STAT6 axis to reduce M2 polarization	[55,56]
IL-15	IL-2 Family	UUO mouse model; CKD model	AMPK pathway	AMPK, glycolysis-related genes	Regulates macrophage metabolic reprogramming (glycolysis); inhibits M1 macrophage polarization	Prevents renal fibrosis by inhibiting collagen synthesis and macrophage infiltration; endogenous IL-15 decreases in CKD	[57]
IL-34	Other interleukins	CKD mouse model; Renal fibrosis model	YAP/Hippo pathway	YAP, integrin αvβ6	Secreted by tubular epithelial cells via αvβ6/YAP axis; promotes macrophage migration and pro-inflammatory differentiation	Mediates renal inflammation and macrophage infiltration; αvβ6 knockout reduces IL-34 secretion and renal injury	[28]
IL-18	IL-1 Family	Gouty nephropathy model; AKI-CKD model	NLRP3 inflammasome pathway	NLRP3, caspase-1	Co-activated with IL-1β by NLRP3 inflammasome; promotes M1 macrophage polarization and inflammatory cascade	Exacerbates renal inflammatory injury; mitochondrial protection inhibits IL-18 upregulation and arrests CKD	[49]

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney injury; UUO, unilateral ureteral obstruction.

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and IL-1β can markedly amplify the effect of M1 polarization. This interaction plays a critical part in the transition from ischemia-reperfusion injury to CKD.[49]

IL-6 and IL-11 from the IL-6 family act as core amplifiers for M1 polarization of macrophages.[33,52] IL-6 promotes macrophage polarization toward the M1 phenotype by binding to the gp130 receptor and activating the STAT3 pathway.[77] It also inhibits the secretion of IL-10 and forms an inflammatory amplification loop.[4,26] As an important member of the IL-6 family, IL-11 not only drives M1 polarization of macrophages by activating the STAT3/ERK1/2 pathway. It also induces the transformation of macrophages into myofibroblasts and exerts dual effects of pro-inflammation and pro-fibrosis.[52,78]

Other pro-inflammatory interleukins including IL-17 and IL-34 also exert important regulatory functions. IL-17 promotes macrophage M1 polarization by activating the NF-κB and MAPK pathways and accelerates glomerulosclerosis in diabetic nephropathy.[48] IL-34 is secreted by renal tubular epithelial cells. It specifically induces macrophage polarization toward the M1 phenotype by activating the Hippo/YAP pathway. Its expression level is positively correlated with the degree of macrophage infiltration in renal tissues from patients with CKD.[28,79]

Anti-inflammatory interleukins induce the transformation of macrophages into the protective M2 phenotype and restore polarization balance by activating protective signaling pathways. IL-4 from the IL-2 family acts as a classic inducer of macrophage M2 polarization. It activates the STAT6 pathway by binding to the IL-4Rα receptor, upregulates the expression of M2 markers including CD206 and Arg-1, and suppresses the secretion of pro-inflammatory cytokines.[56,65] IL-4 can also enhance the stability of M2 polarization by regulating lipid metabolism in macrophages and shows renoprotective effects in lupus nephritis.[71]

IL-10 and IL-22 from the IL-10 family function as key negative regulators in maintaining the balance of macrophage polarization.[80] IL-10 directly blocks M1 polarization of macrophages by inhibiting the NF-κB and MAPK pathways, and promotes the differentiation of the M2c subset at the same time. This subset mainly exerts anti-inflammatory effects without obvious pro-fibrotic activity.[4,21] IL-22 regulates metabolic reprogramming of macrophages by activating the AMPK pathway. It inhibits M1 polarization and facilitates protective M2 polarization. IL-22 also enhances the regenerative capacity of renal tubular epithelial cells and plays a critical protective role in the transition from AKI to CKD.[81,82]

IL-33 and IL-1Ra from the IL-1 family achieve balanced restoration through distinct mechanisms. IL-33 induces macrophage polarization toward the M2 phenotype by binding to the ST2 receptor. It can alleviate renal tubular injury and collagen deposition in the UUO model.[31,54] As an IL-1 receptor antagonist, IL-1Ra blocks IL-1β mediated M1 polarization by competitively binding to the IL-1R1 receptor. It exhibits anti-inflammatory effects in hyperuricemic nephropathy.[20,83]

The Vicious Cycle Between Macrophage Polarization and Interleukins: A Core Closed Loop in CKD Progression

The vicious cycle formed between aberrant macrophage polarization and dysregulated interleukin networks represents the core pathological closed loop driving the continuous progression of CKD. Initiation of this closed loop begins with initial renal injury. Injured renal tubular epithelial cells secrete pro-inflammatory factors such as IL-1β and IL-34, which recruit peripheral blood monocytes to infiltrate and differentiate into macrophages.[28,29] These macrophages are induced by pro-inflammatory cytokines to polarize toward the M1 phenotype and become the major source of interleukin secretion.

Pro-inflammatory cytokines secreted by M1 macrophages, including IL-1β, IL–6 and IL-18, further stabilize the M1 phenotype through autocrine signaling and form a self-feedback loop of polarization and inflammation.[32] These cytokines also act on neighboring monocytes and macrophages via paracrine pathways to induce their polarization toward the M1 phenotype and amplify the inflammatory response.[4] Meanwhile, these pro-inflammatory cytokines aggravate the damage to resident renal cells. This stimulates the cells to secrete more pro-inflammatory cytokines and chemokines, which recruit additional monocytes for infiltration and establish a cycle of injury, recruitment, polarization and re-injury.[84]

As the disease progresses, this closed loop gradually evolves toward fibrosis. IL–6 secreted by M1 macrophages induces pathological deviation of M2 macrophages.[52] TGF-β secreted by pathological M2 macrophages not only accelerates renal fibrosis but also induces fibroblasts to secrete more TGF-β, which further drives the pathological

deviation of M2 macrophages.[12] In addition, IL-33 secreted by pathological M2 macrophages regulates the phenotype of surrounding macrophages via paracrine signaling and promotes their transformation into pro-fibrotic subsets.[55]

This vicious cycle shares similar core mechanisms across different etiologies of CKD but exhibits etiology-specific regulatory nodes. In diabetic nephropathy, the high-glucose environment activates this closed loop via the TLR4 pathway.[30] In hypertensive renal injury, high-salt intake initiates the loop through the TonEBP pathway.[85] In autoimmune kidney disease, autoantibodies trigger the loop by activating the complement system.[53] Breaking this vicious cycle has become a core target for CKD treatment, and targeting the interleukin network to reshape the balance of macrophage polarization represents the key strategy to block this closed loop.[20,21]

Core Mechanisms of Interleukin-Mediated Macrophage Polarization Regulation in the Treatment of CKD

Targeting Pro-Inflammatory Interleukins: Blocking the Abnormal Polarization-Inflammation-Fibrosis Pathway

Targeting pro-inflammatory interleukins and their downstream signaling pathways can directly block macrophage M1 polarization and break the pathological chain of "pro-inflammation–abnormal polarization–fibrosis", which represents the most extensively investigated therapeutic mechanism to date. This mechanism is mainly achieved by neutralizing pro-inflammatory cytokines, blocking interleukin receptors, and inhibiting downstream signaling pathways (Figure 2).

Neutralization of pro-inflammatory interleukins directly reduces their concentration in the renal microenvironment and inhibits M1 polarization of macrophages. Anti IL-1β neutralizing antibodies can markedly attenuate M1 polarization of macrophages in hyperuricemic nephropathy, decrease the expression of IL-6 and TNF-α in renal tissue, and alleviate renal inflammation and fibrosis.[30,83] Anti IL-11 neutralizing antibodies block IL-11 mediated activation of the STAT3

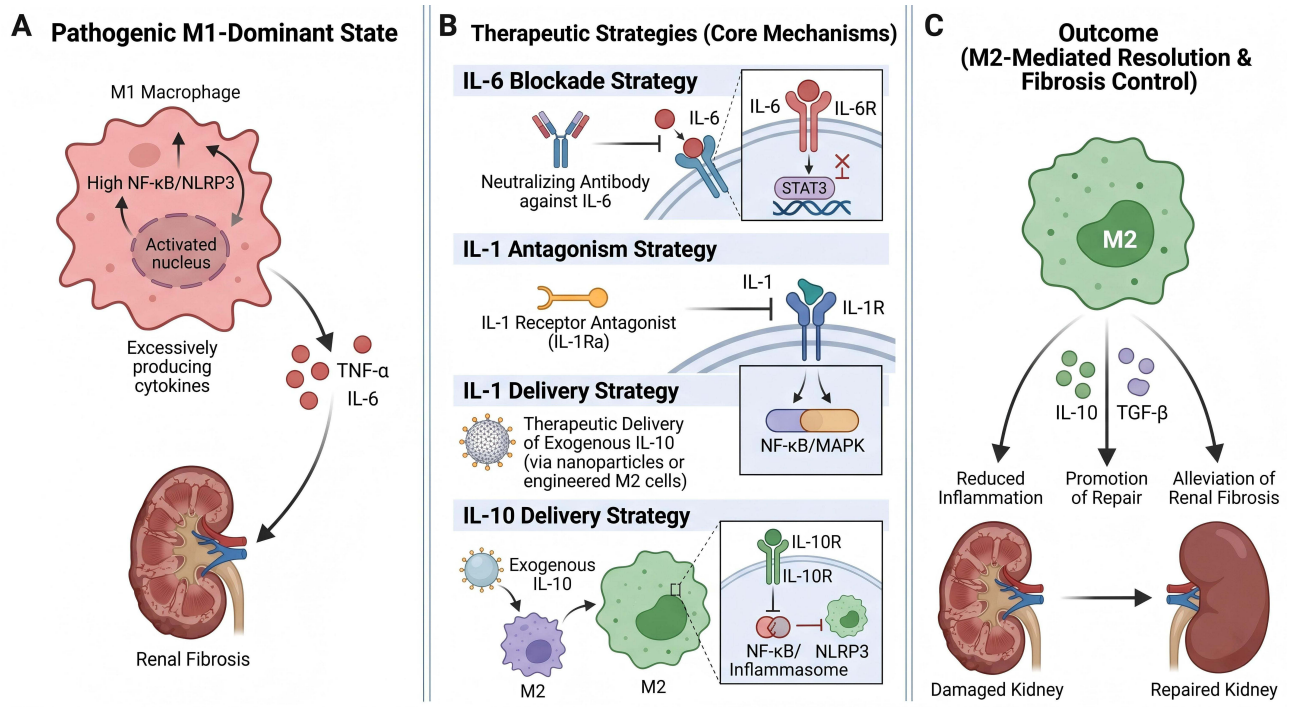

Figure 2 Core mechanisms of interleukin-mediated macrophage polarization regulation in CKD treatment. (**A**) Pathogenic M1-dominant state. In the diseased renal microenvironment, M1 macrophages overactivated via the NF-κB pathway and NLRP3 inflammasome hypersecrete pro-inflammatory cytokines (TNF-α, IL-6), driving structural damage and renal fibrosis. (**B**) Therapeutic strategies. Targeted interventions interrupt the inflammatory cycle by modulating interleukin pathways. IL-6 neutralizing antibodies and IL-1 receptor antagonists (IL-1Ra) block IL-6R and IL-1R, respectively, inhibiting downstream pro-inflammatory signaling (eg, STAT3). Additionally, nanocarrier-mediated delivery of exogenous IL-10 activates IL-10R, suppressing NF-κB/MAPK and NLRP3 inflammasome pathways to drive the M1-to-M2 phenotypic transition. (**C**) Outcome. Repolarized M2 macrophages secrete regulatory factors (IL-10, TGF-β), reducing inflammation and facilitating fibrosis resolution. Arrows (→) indicate directional process flow or phenotypic transition; T-shaped lines (—|) represent pharmacological blockade or biological inhibition; red crosses (X) denote targeted signaling suppression.

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pathway and reverse M1 polarization of macrophages and myofibroblast transformation, showing favorable anti-fibrotic effects in CKD animal models.[52,78] These studies confirm that direct neutralization of pro-inflammatory interleukins can precisely target abnormal macrophage polarization and exert renoprotective effects.

Blockade of interleukin receptors inhibits pro-inflammatory signal transduction at the source. IL-6 receptor antagonists can block the binding of IL-6 to the gp130 receptor, suppress the activation of the STAT3 pathway, and reduce M1 polarization of macrophages, thereby alleviating renal inflammation in both diabetic nephropathy and salt-sensitive hypertensive renal injury.[26,29] IL-1R1 antagonists competitively bind to the IL-1R1 receptor, block the signal transduction of IL-1β, inhibit the activation of the NLRP3 inflammasome, and reduce the release of pro-inflammatory factors related to M1 polarization of macrophages.[32,47]

Inhibition of downstream signaling pathways of pro-inflammatory interleukins enables multi-target anti-inflammatory effects. The NLRP3 inflammasome serves as a core upstream pathway for the release of IL-1β and IL-18. Inhibitors such as MCC950 and 1,3-butanediol can reduce the release of pro-inflammatory interleukins and reverse M1 polarization of macrophages by suppressing NLRP3 activation, thus exerting protective effects in renal calcification-related CKD and hyperuricemic nephropathy.[11,86] The NF-κB pathway acts as a common downstream pathway through which various pro-inflammatory interleukins regulate macrophage polarization. Inhibitors of this pathway can simultaneously block IL-1β, IL-6 and IL-17 mediated M1 polarization and exert synergistic anti-inflammatory effects in multiple CKD models.[87,88]

Enhancing Anti-Inflammatory Interleukins: Activating the Balanced Polarization-Repair Pathway

Enhancing the expression or activity of anti-inflammatory interleukins can induce the transformation of macrophages into the protective M2 phenotype, restore polarization balance, and achieve the dual effects of renal inflammation resolution and tissue repair.[37] The core of this mechanism lies in improving the targeted delivery efficiency and stability of anti-inflammatory interleukins to avoid their rapid degradation in vivo.

Direct supplementation of anti-inflammatory interleukins represents the most direct intervention approach, yet it is confronted with the problem of low bioavailability. As a classic anti-inflammatory interleukin, IL-10 is prone to degradation upon direct administration, and systemic administration may increase the risk of infection. Studies have demonstrated that IL-10 delivery via exosomes can significantly improve its stability and renal targeting ability. Targeting molecules on the exosome surface enable its specific enrichment in renal macrophages, efficiently driving M2 polarization and successfully preventing the transition from AKI to CKD in ischemia-reperfusion injury models.[21]

Local delivery of IL-33 also exhibits favorable effects. Local injection of IL-33 into renal tissue can specifically induce macrophage M2 polarization and alleviate chronic rejection after renal transplantation.[55] Upregulating the expression of endogenous anti-inflammatory interleukins is a strategy with greater potential for clinical translation. Active components of TCM such as paeoniflorin can upregulate the expression of IL-10 in macrophages via KLF4-mediated mitophagy, induce M2 polarization, and alleviate renal inflammation and fibrosis.[4,65] Astragaloside IV can promote the secretion of IL-4 by macrophages through regulating the PPARγ pathway, enhance the stability of M2 polarization, and protect podocytes in diabetic nephropathy.[71] SGLT2 inhibitors can upregulate the expression of IL-22 in renal tissue by activating the AMPK pathway, induce the transformation of macrophages into the protective M2 phenotype, and exert cardiorenal protective effects.[5,89]

Activation of downstream signaling pathways of anti-inflammatory interleukins can amplify their regulatory effects. STAT6 serves as the core downstream pathway through which IL-4 and IL-33 regulate macrophage M2 polarization. Activators of STAT6 can directly induce macrophage polarization toward the M2 phenotype without relying on the supplementation of exogenous interleukins.[56,90] The AMPK pathway acts as a key pathway for IL-22 to regulate macrophage polarization. AMPK activators such as metformin can synergize with IL-22 to induce protective M2 polarization by enhancing the activity of this pathway, exerting dual effects of metabolic intervention and immune regulation in CKD.[13,82]

Regulating Metabolic Reprogramming: A New Dimension of Interleukin-Mediated Macrophage Polarization Regulation

Interleukins affect the polarization state of macrophages by regulating their metabolic reprogramming, and this mechanism provides a new direction for metabolic-immune combined intervention in the treatment of CKD. Macrophage polarization is closely related to metabolic patterns. M1 macrophages rely primarily on glycolysis as their main metabolic mode, whereas M2 macrophages depend on oxidative phosphorylation.[91] The interleukin network achieves precise regulation of polarization by modulating this metabolic switch.

Pro-inflammatory interleukins predominantly promote macrophage M1 polarization by enhancing glycolysis and inducing mitochondrial dysfunction.[92,93] IL-1β and IL-6 upregulate the expression of key glycolytic enzymes including HK2 and PFKFB3, strengthen the glycolytic capacity of macrophages, and provide energy and metabolic intermediates for M1 polarization.[13,94] Meanwhile, these pro-inflammatory interleukins trigger the production of mitochondrial reactive oxygen species, activate the NLRP3 inflammasome, and further amplify the effect of M1 polarization.[49] In diabetic nephropathy, the synergistic action of high-glucose environment and IL-6 exacerbates abnormal glycolysis in macrophages and drives the sustained activation of M1 polarization.[30]

Anti-inflammatory interleukins induce macrophage M2 polarization by promoting oxidative phosphorylation and mitochondrial repair.[95] IL-4 and IL-10 upregulate the expression of proteins related to mitochondrial oxidative phosphorylation such as PGC-1α, enhance mitochondrial energy metabolism, and provide support for M2 polarization.[49,71] IL-4 can also enhance the antioxidant capacity of macrophages by regulating sphingolipid metabolism and maintain the stability of M2 polarization.[90] IL-22 promotes mitophagy, repairs damaged mitochondria, restores the metabolic balance of macrophages by activating the AMPK pathway, and further induces protective M2 polarization.[81,82]

Targeting metabolic reprogramming in macrophages can synergize with interleukin regulation to modulate their polarization state. LXR/PPARγ agonists can reverse IL-6-mediated M1 polarization by improving cholesterol efflux in macrophages and suppressing abnormal glycolysis.[94] Mitochondrial protectants such as SS-31 can reverse M1 polarization of macrophages and halt CKD progression by inhibiting mitochondrial ROS production and reducing the release of IL-1β and IL-18.[49] These studies confirm that the combined use of metabolic intervention and interleukin-targeted therapy can generate synergistic effects and enhance therapeutic efficacy.[13]

Downstream Dual Therapeutic Effects: Simultaneous Achievement of Anti-Inflammatory and Anti-Fibrotic Functions

The core advantage of interleukin-mediated regulation of macrophage polarization in CKD treatment is that it can simultaneously exert dual therapeutic effects of anti-inflammation and anti-fibrosis, which is difficult to achieve with current therapeutic methods. These dual effects result from the comprehensive functional remodeling of macrophages after the restoration of polarization balance.

In terms of anti-inflammation, restoration of polarization balance can markedly reduce renal inflammatory infiltration and the release of pro-inflammatory factors. After targeting pro-inflammatory interleukins to block M1 polarization, the infiltration level of $CD86^+$ macrophages in renal tissue is significantly decreased, and the expression levels of pro-inflammatory factors including IL-1β, IL-6 and TNF-α are substantially reduced.[4,78] Following enhancement of anti-inflammatory interleukins to induce M2 polarization, IL-10 secreted by protective M2 macrophages can inhibit T cell activation and attenuate the amplification of adaptive immune responses, which is particularly important in autoimmune kidney disease.[65] Meanwhile, the restoration of polarization balance can suppress macrophage pyroptosis, reduce the passive release of inflammatory factors, and further alleviate renal inflammation.[63]

In terms of anti-fibrosis, restoration of polarization balance can block the progression of renal fibrosis through multiple links. First, inhibition of pro-inflammatory factors secreted by M1 macrophages reduces renal tubular epithelial-mesenchymal transition and activation of fibroblasts.[11] Second, correction of the pathological deviation of M2 macrophages restores their anti-inflammatory and reparative functions, and decreases the secretion of pro-fibrotic factors such as TGF-β.[12] Third, suppression of the transformation of macrophages into myofibroblasts lowers the direct deposition of

extracellular matrix.[43,55] Fourth, protective M2 macrophages can degrade deposited extracellular matrix by secreting matrix metalloproteinases, thereby achieving fibrosis regression.[81]

Multiple studies have validated such dual therapeutic effects: paeoniflorin alleviates renal inflammation while significantly reducing the expression of fibrotic markers including collagen I and α-SMA by regulating the balance of macrophage polarization.[4] SGLT2 inhibitors not only improve the microinflammatory state in patients with CKD but also delay the progression of renal fibrosis by promoting macrophage M2 polarization.[5,89] IL-10-loaded exosomes simultaneously achieve renal inflammation resolution and tissue repair after ischemia-reperfusion injury following the induction of macrophage M2 polarization.[21] These dual effects suggest that therapeutic strategies targeting the interleukin–macrophage polarization axis can fundamentally block the pathological progression of CKD.

Research Status and Characteristics at Home and Abroad

International Research Progress: Precision Biologic Development and in-Depth Mechanistic Analysis

In the field of interleukin-mediated regulation of macrophage polarization for CKD treatment, international research is characterized by the development of precision biologics, in-depth dissection of molecular mechanisms and exploration of targeted delivery technologies, with a focus on fibrosis reversal and clinical translation. In terms of biologic development, monoclonal antibodies targeting pro-inflammatory interleukins are research hotspots. Tocilizumab, an anti-IL-6R monoclonal antibody, has entered Phase II clinical trials for diabetic nephropathy. Studies have confirmed that it can significantly reduce the proportion of M1 macrophages in peripheral blood and decrease the urinary albumin excretion rate in patients.[96] Canakinumab, an anti-IL-1β monoclonal antibody, has shown effects in inhibiting macrophage M1 polarization and alleviating renal injury in preclinical studies of hyperuricemic nephropathy, and is currently in Phase I clinical research.[83] As a novel targeted drug, neutralizing antibody against IL-11 has successfully reversed abnormal macrophage polarization and renal fibrosis in CKD animal models, becoming a new research direction in this field.[78,83]

In terms of mechanistic dissection, international studies have delved into the levels of transcriptional regulation, epigenetics and metabolic reprogramming. Studies have identified the central role of the STAT3/STAT6 pathway in interleukin-mediated regulation of macrophage polarization, and revealed that downstream transcription factors such as IRF4 and KLF4 can precisely control the M1/M2 phenotypic switch.[4,43] Breakthroughs have been made in the research of epigenetic regulatory mechanisms. It has been found that the histone demethylase Jmjd3 can modulate the transformation of macrophages into myofibroblasts by regulating the expression of IRF4.[43] Research on the mechanisms of metabolic reprogramming is becoming increasingly in-depth, clarifying the molecular pathways through which interleukins influence macrophage polarization by regulating glycolysis, lipid metabolism and mitochondrial function.[13,71]

In terms of targeted delivery technology, international research is devoted to the development of renal macrophage-specific delivery systems. Mannose receptor-modified liposomes can specifically bind to the CD206 receptor on the macrophage surface to achieve targeted delivery of interleukin inhibitors. In diabetic nephropathy models, this delivery system can significantly improve the renal accumulation of drugs and reduce systemic side effects.[21] The application of nanobody technology has greatly reduced the molecular weight of interleukin-targeted drugs, enhanced their tissue penetration, and allowed them to reach renal lesions more efficiently.[57] The development of these technologies has laid a foundation for the clinical translation of interleukin-targeted therapy.

Domestic Research Progress: Regulation by Natural Products and Translational Research of Integrated Traditional Chinese and Western Medicine

Domestic research in this field is characterized by the regulation of natural products from TCM, integrated traditional Chinese and Western medicine therapy, and clinical cohort studies. It has formed a research system complementary to international research, focusing on clinical practicability and multi-target synergistic therapy.

In terms of regulation by natural products from TCM, Chinese scholars have screened a large number of active components and compound prescriptions that modulate the interleukin–macrophage polarization axis. Active TCM components such as paeoniflorin, emodin and astragaloside IV remodel the balance of macrophage polarization through

multi-target regulation of the interleukin network.[4,40,71] Paeoniflorin upregulates IL-10 expression and inhibits IL-6 secretion via KLF4-mediated mitophagy, inducing macrophage M2 polarization.[4] Emodin reduces the release of IL-1β by suppressing the EGFR/MAPK pathway, blocking macrophage M1 polarization.[40] Astragaloside IV promotes IL-4 secretion and enhances the stability of M2 polarization by regulating the PPARγ pathway.[71]

TCM compound prescriptions such as the Astragalus-Panax Notoginseng compound and Guben Xiezuo Decoction restore macrophage polarization balance through synergistic regulation of multiple interleukins.[79,97] The Astragalus-Panax Notoginseng compound inhibits the Mincle signaling pathway, downregulates the expression of IL-1β and IL-6, reduces macrophage M1 polarization, and alleviates cisplatin-induced renal injury.[79]

In terms of integrated traditional Chinese and Western medicine therapy, domestic studies have confirmed that TCM can synergize with basic Western medicine treatments to improve the therapeutic efficacy of CKD. The combined application of SGLT2 inhibitors and Astragalus membranaceus can enhance macrophage M2 polarization by synergistically regulating the expression ratio of IL-6/IL-10, and improve renal function in patients with diabetic nephropathy more effectively than monotherapy.[5,89]

Glucocorticoids combined with total glucosides of paeony (TGP) in the treatment of lupus nephritis can reduce the dosage and side effects of glucocorticoids by synergistically inducing macrophage M2 polarization.[65] These studies confirm that integrated traditional Chinese and Western medicine therapy can break through the limitations of monotherapy through multi-target synergy and possesses significant clinical advantages.

In terms of clinical and translational research, Chinese scholars have carried out cohort studies on macrophage polarization phenotypes in Chinese CKD populations, and clarified the characteristics of interleukin expression profiles in CKD patients with different etiologies. Diabetic nephropathy is characterized by high expression of IL-6 and IL-17, while IgA nephropathy is featured by imbalanced expression of IL-33 and IL-10, providing a basis for individualized treatment.[37,45] Meanwhile, Chinese scholars are devoted to the standardization and targeted delivery research and development of active ingredients from TCM. The development of astragalus polysaccharide-chitosan microspheres has improved the renal targeting and bioavailability of astragalus polysaccharide, and enhanced its effect in regulating the interleukin–macrophage polarization axis.[71] These studies provide important support for the clinical translation of natural products from TCM.

Challenges and Future Perspectives

Core Challenges in Clinical Translation

Macrophage polarization heterogeneity is the primary challenge facing current clinical translation. CKD has complex etiologies, and marked differences exist in the renal microenvironment among CKD cases with different causes, including diabetic nephropathy, hypertensive renal injury, autoimmune nephropathy and obstructive nephropathy, leading to etiology-specific polarization phenotypes of macrophages. Diabetic nephropathy is dominated by excessive activation of M1 macrophages, obstructive nephropathy is featured by the enrichment of pathological M2 macrophages, and lupus nephritis presents a mixed M1/M2 polarization imbalance.[44,54]

Even in CKD with the same etiology, the polarization phenotypes vary across different disease stages. The early stage is dominated by M1 polarization, the middle stage manifests an imbalanced M1/M2 polarization, and the advanced stage is centered on pathological M2 polarization.[14]

In addition, individual differences such as age, gender and genetic background can also affect the polarization phenotypes of macrophages and the expression profile of interleukins.[14] Current single interleukin-targeted therapy cannot adapt to such highly heterogeneous polarization characteristics, leading to a limited therapeutic response rate, and even treatment failure or disease aggravation in some patients.[44]

Another core challenge for clinical translation is the insufficient renal targeting precision of existing interleukin-targeted drugs. Interleukins and their receptors are expressed in multiple tissues and organs throughout the body. Upon systemic administration, drugs act nonspecifically on systemic immune cells, resulting in severe systemic side effects. Anti-IL-6R monoclonal antibodies may increase infection risk and cause blood glucose fluctuations.[96] Systemic administration of IL-10 may suppress antitumor and anti-infective immunity, raising the risk of malignancies and infections.[21]

Although certain progress has been made in targeted delivery technologies, numerous limitations still remain. Mannose receptor-modified delivery systems can only target M2 macrophages but fail to act on M1 macrophages.[21] Nanocarriers show insufficient in vivo stability and are readily cleared by the mononuclear phagocyte system. Local administration approaches such as renal artery injection and renal parenchymal injection are invasive and difficult to be routinely applied in clinical settings. The key to overcoming this challenge is to develop delivery systems with dual M1/M2 macrophage targeting, high stability and minimal invasiveness.

Renal fibrosis represents the core endpoint of CKD progression, yet the limitations in its evaluation make it difficult to objectively determine the therapeutic efficacy of interleukin-targeted therapy. Current clinically used methods for fibrosis assessment, including renal pathological biopsy, detection of serum fibrosis markers and imaging examinations, all have obvious shortcomings. Renal pathological biopsy is an invasive procedure that is difficult to perform repeatedly, making it impossible to dynamically monitor therapeutic effects. Serum fibrosis markers such as collagen I and α-SMA lack sufficient specificity and sensitivity, and cannot reflect local renal fibrotic changes.[12] Existing imaging modalities such as ultrasound, CT and MRI cannot accurately detect early alterations in renal fibrosis.

Such limitations in evaluation make it difficult for clinical studies to objectively determine the ameliorative effect of interleukin-targeted therapy on renal fibrosis, so that only indirect assessment can be carried out relying on renal function indicators such as eGFR and urinary albumin/creatinine ratio (UACR). However, changes in renal function indicators are lagging and cannot timely reflect the impact of treatment on the core pathological process.[5] The development of sensitive, specific and non-invasive assessment methods for renal fibrosis is an important prerequisite to promote the clinical translation of interleukin-targeted therapy.

The ambiguous mechanism and lack of standardization in the regulation of the interleukin–macrophage polarization axis by natural products from TCM represent the core bottleneck for the clinical translation of domestic research. Most studies have only verified the therapeutic effects of active ingredients or compound prescriptions from TCM, but have not clarified their specific molecular targets. For instance, the specific receptor through which astragalus polysaccharide regulates IL-4 secretion and the molecular mechanism by which paeoniflorin activates KLF4 have not been clearly elucidated.[4,71]

Beyond efficacy and safety, the high economic burden of interleukin-targeted biologics emerges as a critical barrier to large-scale clinical translation and widespread application in CKD management. Monoclonal antibodies such as tocilizumab and canakinumab, which have advanced to clinical trials for CKD-related complications, incur substantial annual treatment costs.[22] These expenses are particularly prohibitive for low- and middle-income regions with high CKD prevalence, limiting accessibility for most patients. Additionally, the long-term administration required for chronic CKD further amplifies economic pressure. While natural products and traditional Chinese medicine-derived interventions offer cost-effective alternatives, their standardization and large-scale production still require cost optimization. Collectively, economic feasibility remains a key determinant for translating interleukin-targeted strategies from research to routine clinical practice.

The ambiguity of mechanisms renders the therapeutic targets of natural products from TCM undefined, which hinders standardized production and quality control. Active components derived from TCM of different origins and extraction processes exhibit remarkable differences in their regulatory effects on the interleukin network. Meanwhile, the multi-component and multi-target properties of TCM compound prescriptions further complicate the mechanistic dissection, making it difficult to meet the standards required for international clinical trials. Clarifying the core therapeutic targets of TCM via multi-omics technologies and achieving standardized production is the key to advancing the clinical translation of natural products from TCM.

Future Research Directions

Precision classification based on macrophage polarization phenotypes and interleukin expression profiles is the core direction for the development of future therapeutic strategies. In the future, large-scale CKD clinical cohort studies should be conducted, integrating technologies such as single-cell sequencing and flow cytometry to establish macrophage polarization phenotype maps and interleukin expression profiles of CKD patients with different etiologies and stages. This will clarify the clinical characteristics and therapeutic targets of different subtypes, including the "M1-dominant type", "abnormal M2-dominant type" and "mixed type".[37,45]

Multi-target combined therapeutic strategies will be developed to suit different CKD subtypes. Kidney disease driven primarily by M1 polarization will be treated with a combined regimen of anti-IL-1β monoclonal antibodies and NLRP3 inhibitors that exerts dual blockade on the upstream signaling pathways of M1 polarization.[20,47] CKD characterized by predominant abnormal M2 polarization will receive a combined regimen of IL-10-loaded exosomes and TGF-β inhibitors which restores the reparative function of M2 macrophages.[21,43] Mixed-type CKD will be managed with a combined regimen of anti-IL-6 monoclonal antibodies and IL-22 agonists that modulates pro-inflammatory and anti-inflammatory interleukin networks simultaneously.[81,96] The integration of such precise subtyping and combined therapy can markedly elevate the therapeutic response rate and realize individualized treatment for patients.

Developing kidney macrophage-specific delivery systems with high targeting specificity, high stability, and minimal invasiveness is the core approach to addressing systemic side effects. Future research should focus on the screening of novel targeting molecules and the optimization of delivery carriers. Screen macrophage-specific surface markers such as TREM2 and CSF1R, develop their specific antibodies or peptides to achieve dual targeting of both M1 and M2 macrophages.[57] Optimize the structure of nanocarriers (eg, adopting red blood cell membrane-coated nanocarriers) to enhance their in vivo stability and avoid clearance by the mononuclear phagocyte system. Integrate minimally invasive drug delivery technologies such as ultrasound-guided microbubble delivery systems to realize non-invasive and precise drug delivery.

Meanwhile, intelligent responsive delivery systems can be developed to enable specific drug release in the pathological microenvironment of CKD. For instance, in response to the low pH and high reactive oxygen species (ROS) characteristics of the renal microenvironment in CKD, pH-sensitive and ROS-sensitive nanocarriers can be designed to release drugs exclusively at renal lesion sites, further improving targeting specificity and therapeutic efficiency.[90] These innovations in delivery systems will provide technical support for the clinical application of interleukin-targeted therapy.

In addition to renal fibrosis, pulmonary hypertension (PH) represents a severe, underrecognized comorbidity of CKD. In a retrospective study of Chinese patients, it was shown that up to 18.1% of CKD patients develop PH, which significantly increases cardiovascular mortality. Although hemodynamic stress and volume overload contribute to PH pathogenesis, emerging evidence highlights a shared inflammatory and immune mechanism involving dysregulated macrophage polarization. In PH, the pulmonary microenvironment drives a pro-inflammatory M1 macrophage phenotype, which secretes high levels of IL-1β, IL-6, and TNF-α to promote vascular remodeling and right ventricular hypertrophy. Conversely, restoring an M2-like anti-inflammatory phenotype has shown protective effects in experimental PH models. Given the central role of the interleukin-macrophage polarization axis in both CKD and PH, targeting this common immune pathway may provide a novel therapeutic strategy to treat or prevent PH in CKD patients, warranting future translational research.

Multidisciplinary collaboration will be adopted to dissect the molecular mechanisms underlying the regulation of the interleukin–macrophage polarization axis by natural products from TCM, and to realize their standardization and clinical translation, which constitutes the core development direction of domestic research. In the future, multi-omics technologies including transcriptomics, proteomics and metabolomics will be integrated to screen the core therapeutic targets of TCM active ingredients:surface plasmon resonance technology will be used to clarify the binding modes of TCM active ingredients with interleukin receptors and downstream signaling molecules; gene editing technology will be applied to verify the functions of the targets.[4,71]

Based on mechanistic elucidation, standardized production of natural products from TCM will be achieved. Quality control standards for the active ingredients of TCM will be formulated to specify the content, purity and stability of their effective components. Derivatives of these active ingredients will be created including the structural modification of paeoniflorin to enhance their bioavailability and targeting capacity.[4] In the meantime, multicenter, randomized and double-blind clinical trials will be launched to validate the safety and efficacy of natural products from TCM and their compound prescriptions for the treatment of CKD. A comprehensive evaluation system that integrates renal function indicators, inflammatory and fibrotic markers and renal pathological biopsy will be employed to objectively assess the therapeutic efficacy.[5]

Focusing on the early intervention of CKD and establishing a multidisciplinary collaborative research system are crucial for delaying CKD progression and reducing the incidence of end-stage renal disease (ESRD). In the future, early

intervention strategies for high-risk populations of CKD (such as patients with diabetes and hypertension) should be explored. By detecting macrophage polarization markers and interleukin expression profiles in peripheral blood, high-risk individuals for CKD can be identified. Low-dose SGLT2 inhibitors, TCM Astragalus membranaceus, and other interventions can be used for early intervention to remodel the balance of macrophage polarization and delay the onset of CKD.[5,71]

Establishing a multidisciplinary collaborative research system will integrate the advantages of multiple disciplines including nephrology, immunology, natural medicinal chemistry, nanotechnology, and bioinformatics. Specialists in nephrology and immunology are responsible for clinical cohort studies and mechanistic dissection;experts in natural medicinal chemistry oversee the screening and standardization of active components from TCM. Nanotechnology experts lead the development of targeted delivery systems. Bioinformatics experts undertake the analysis of polarization phenotype maps and interleukin expression profiles. This multidisciplinary collaborative research system can accelerate the translation of basic research to clinical practice, and promote interleukin-targeted therapy to become a novel standard treatment regimen for CKD. Prioritizing large-scale, multicenter clinical cohort studies is the most urgent step to establish etiology- and stage-specific macrophage polarization subtypes, laying a solid foundation for precision therapy. Accelerating the development of dual M1/M2 macrophage-targeted delivery systems is another critical priority to overcome systemic side effects and improve therapeutic efficacy.[98]

Conclusion

CKD is characterized by a core pathological loop consisting of renal injury, interleukin network imbalance, macrophage polarization disorder, inflammation, and fibrosis. As a key regulatory hub, interleukins precisely modulate macrophage polarization balance and thus emerge as a core target for intervening in CKD progression.

At the mechanistic level, pro-inflammatory interleukins including IL-1β, IL-6, and IL-17 activate the NF-κB and STAT3 pathways. This activation drives excessive polarization of macrophages toward the M1 phenotype, which then secrete large amounts of pro-inflammatory factors to exacerbate renal parenchymal injury. Anti-inflammatory interleukins such as IL-4, IL-10, and IL-22 induce protective M2 polarization through the STAT6 and AMPK pathways, thereby participating in inflammation resolution and tissue repair. However, in CKD, M2 macrophages undergo pathological deviation, characterized by weakened reparative function and enhanced pro-fibrotic effects. This polarization imbalance and the disordered interleukin network form a vicious cycle that serves as the core driving force for the progressive progression of CKD.

The significance of this research lies in the systematic clarification of the complete molecular network through which the interleukin-macrophage polarization axis regulates the renal inflammatory microenvironment. It addresses the limitations of single-target research and provides a dual intervention strategy encompassing upstream anti-inflammation and downstream anti-fibrosis for CKD. International research focuses on the precise targeting of biological agents, such as anti-IL-6R monoclonal antibodies, while domestic research delves into the multi-target regulation of active components from TCM, including paeoniflorin and astragaloside IV. These two research directions form complementary advantages. Despite facing challenges such as polarization heterogeneity and insufficient targeting accuracy, breakthroughs in precise typing, multi-target combination therapy, and targeted delivery technologies are expected to enable this regulatory axis to become a new platform for the precise treatment of CKD, offering new hope for improving patient prognosis. Notably, such precision interventions hold the potential to reduce the global burden of end-stage renal disease (ESRD) and alleviate the substantial healthcare costs associated with dialysis and renal transplantation, highlighting the critical real-world clinical and public health significance of this research.[1,3]

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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