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Diagnostic and therapeutic potential of interleukin-37 in kidney diseases: A mini-review

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Abstract. *Interleukin-37 (IL-37) is a newly discovered anti-inflammatory cytokine from the IL-1 family that plays a key role in regulating both innate and adaptive immune responses. It is secreted in healthy tissues, reflecting a homeostatic function. Intracellularly, IL-37 suppresses diverse inflammatory signals in various cells, including dendritic cells, macrophages, epithelial cells, and endothelial cells. Although it has been studied in many conditions, such as autoimmune disorders, cancer, and cardiovascular disease, its specific role in kidney diseases remains relatively understudied.*

In this mini-review, we summarize current evidence on the biology of IL-37, with a focus on its relevance to kidney disease. We explore its molecular structure, patterns of expression, and the immunomodulatory mechanisms that may influence kidney diseases, including acute kidney injury, diabetic nephropathy, and autosomal dominant polycystic kidney disease. We also discuss the challenges of translating IL-37-based therapies into clinical practice and highlight key areas for future research aimed at unlocking its potential in the treatment of kidney diseases.

Key words: *interleukin-37, kidney diseases, acute kidney injury, diabetic nephropathy, autosomal dominant polycystic kidney disease, immunomodulatory mechanisms, interleukin-based therapy.*

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Потенціал інтерлейкіну-37 в діагностиці та лікуванні захворювань нирок: міні-огляд

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Анотація. *Інтерлейкін-37 (ІЛ-37) — це відносно нещодавно відкритий протизапальний цитокін із сімейства ІЛ-1, який відіграє ключову роль у регуляції як вродженої, так і адаптивної імунної відповіді. ІЛ-37 секретується в здорових тканинах, що відображає його гомеостатичну функцію. Внутрішньоклітинно, ІЛ-37 пригнічує запальні сигнали в різних клітинах, включаючи дендритні клітини, макрофаги, епітеліальні клітини та ендотеліальні клітини. Хоча ІЛ-37 ретельно досліджувався при аутоімунних розладах, онкологічних і серцево-судинних захворюваннях, його специфічна роль у патології нирок залишається недостатньо вивченою.*

У цьому міні-огляді ми узагальнюємо сучасні дані щодо біології ІЛ-37, зосереджуючись на його значенні для захворювань нирок. Огляд розглядає його молекулярну структуру, закономірності експресії та імуномодуляторні механізми, які можуть впливати на захворювання нирок, зокрема гостре ураження нирок, діабетичну нефропатію та аутосомно-домінантну полікістозну хворобу нирок. Робота також обговорює виклики впровадження терапії на основі ІЛ-37 у клінічну практику та виділяє ключові напрями для майбутніх досліджень, спрямованих на розкриття потенціалу ІЛ-37 в лікуванні захворювань нирок.

Ключові слова: *інтерлейкін-37, захворювання нирок, гостре ураження нирок, діабетична нефропатія, аутосомно-домінантна полікістозна хвороба нирок, імуномодуляторні механізми, терапія на основі інтерлейкіну.*

Introduction. Kidney diseases, encompassing both acute kidney injury (AKI) and chronic kidney disease (CKD), represent a growing global health burden with significant morbidity, mortality, and socioeconomic impact [1]. Despite advances in understanding the molecular mechanisms underpinning renal pathology, therapeutic options remain largely supportive, and effective biomarkers for early diagnosis and progression monitoring are still limited [2, 3]. In recent years, the role of inflammation in the initiation and progression of kidney diseases has gained increasing attention, opening new avenues for targeted interventions [4, 5]. For example, inflammatory cytokines play a central role in mediating the interplay between metabolic disturbances, such as dyslipidemia, and vascular injury in systemic diseases like diabetes mellitus. A recent study demonstrated that structural changes in the vascular wall and alterations in lipid metabolism are closely linked in diabetic patients, underscoring the importance of inflammatory regulation in cardiorenal pathophysiology [6, 7].

Interleukin-37 (IL-37), a relatively novel member of the IL-1 cytokine family, has emerged as a potent anti-inflammatory and immunomodulatory factor. Unlike classical pro-inflammatory interleukins, IL-37 functions as a natural suppressor of innate and adaptive immune responses [8, 9]. Its expression is elevated in various inflammatory and autoimmune diseases, and preclinical studies suggest a protective role in tissue injury, including renal damage [10, 11]. Moreover, IL-37's dual function, as a secreted cytokine and an intracellular regulator, highlights its unique therapeutic and diagnostic promise [8].

This review aims to synthesize current knowledge on the biology of IL-37, its regulation, and its mechanistic involvement in kidney disease pathophysiology. We explore the potential of IL-37 as a biomarker for disease activity and progression and evaluate emerging evidence supporting its use as a therapeutic agent.

Interleukin-37: structure and function. IL-37 is a unique cytokine encoded by the IL1F7 gene on chromosome 2. It is produced in five isoforms (a–e) through alternative splicing, with IL-37b being the most active and extensively investigated in both healthy and disease states [8, 10]. IL-37 is expressed in a variety of tissues and cell types, including the lymph nodes, thymus, lung, colon, uterus, and bone marrow, as well as in monocytes, epithelial cells, breast carcinoma cells, and endothelial cells. Expression patterns of IL-37 isoforms are tissue-specific and linked to distinct exon usage and protein lengths are presented in Table 1.

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Table 1

Tissue distribution, exon composition, and amino acid lengths of IL-37 isoforms

Isoform	Tissue Distribution	Exons Included	Length (Amino Acids)
IL-37a	Brain	3, 4, 5, 6	192
IL-37b	Kidney, bone marrow, blood, skin, respiratory and urogenital tract	1, 2, 4, 5, 6	218
IL-37c	Heart	1, 2, 5, 6	197
IL-37d	Bone marrow	1, 4, 5, 6	197
IL-37e	Testis	1, 5, 6	157

Abbreviations: IL, interleukin.

Genetic studies indicate that common variants of the IL-37 gene are maintained through balanced selection, though the functional significance of this variability remains to be fully elucidated [**11, 12**]. Notably, some of these variants influence IL-37 protein stability and, consequently, its immune-inhibitory potency [**13, 14**]. These findings suggest a potential link between IL37 genetic variation and susceptibility to various inflammatory or autoimmune conditions.

Structurally, IL-37 adopts the typical β-trefoil fold seen in the IL-1 family but is distinct in its potent anti-inflammatory properties. It functions in both extracellular and intracellular compartments [**10, 12**]. On the cell surface, IL-37 binds to IL-18 receptor α (IL-18Rα) and recruits the co-receptor SIGIRR (also known as IL-1R8), an inhibitor of pro-inflammatory signaling cascades. Intracellularly, IL-37 forms a complex with Smad3, enabling its translocation to the nucleus where it modulates transcriptional programs that attenuate immune responses [**10, 12, 13**].

Functionally, IL-37 downregulates a wide range of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IFN-γ, while enhancing regulatory T cell activity and promoting immune tolerance [**8, 10, 13**]. These properties have been demonstrated across numerous models of inflammation, including gastrointestinal, cardiovascular, autoimmune, and kidney disease [**8, 13**].

IL-37 in acute kidney injury (AKI). IL-37 has shown significant promise as a protective, anti-inflammatory cytokine in the context of AKI, particularly in models of renal ischemia-reperfusion injury (IRI). It reduces the production of key pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6 in response to renal injury [**13, 14**]. These effects are mediated through IL-37's interaction with the interleukin-18 receptor alpha (IL-18Rα) and the co-receptor single immunoglobulin IL-1 receptor-related molecule (SIGIRR/IL-1R8), which collectively inhibit downstream inflammatory signaling [**13, 14**]. Furthermore, IL-37 exerts intracellular effects by binding to Smad3, facilitating its translocation into the nucleus where it modulates transcriptional responses, leading to the suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways [**15**].

In mouse models of renal IRI, overexpression of IL-37 or administration of recombinant IL-37 results in significant reductions in oxidative stress, as evidenced by decreased levels of malondialdehyde (MDA), and in apoptotic signaling, reflected by lower caspase-3 activity [**14**]. These molecular changes correspond with improved histological preservation of renal tissue and enhanced renal function, as indicated by reduced serum creatinine and blood urea nitrogen levels [**14**].

Beyond its role in modulating inflammation and oxidative stress, IL-37 also influences the phenotype of immune cells in the renal microenvironment. It promotes the polarization of macrophages toward the anti-inflammatory M2 phenotype and enhances the activity of tolerogenic dendritic cells, further supporting an immunosuppressive milieu. Additionally, innovative delivery systems such as neutrophil-derived nanovesicles carrying IL-37 have demonstrated the ability to target injured renal endothelial cells [**15**]. This targeted approach reduces leukocyte adhesion and transmigration, promotes angiogenesis, and helps preserve microvascular integrity during IRI.

Transgenic mouse models expressing human IL-37, as well as studies utilizing exogenous IL-37 administration, consistently report improved renal outcomes following AKI. These include diminished inflammatory cytokine levels, reduced cellular injury, and better preservation of renal architecture and function [**14, 16, 17**]. While these findings are currently limited to preclinical studies, they collectively underscore the therapeutic potential of IL-37 in managing AKI, particularly in conditions driven by immune activation and cytokine-mediated damage. A summary of IL-37's effects in AKI models is provided in Table 2.

Table 2

Summary of IL-37's actions in experimental models of AKI [13,15,16]

Mechanism	Effect in AKI models
Suppresses pro-inflammatory cytokines	↓ TNF-α, IL-1β, IL-6, HMGB1
Reduces oxidative stress	↓ Malondialdehyde
Limits apoptosis	↓ Caspase-3 activity
Modulates immune cell phenotypes	↑ M2 macrophages, ↑ tolerogenic dendritic cells
Protects renal endothelium	↓ Leukocyte infiltration, ↑ angiogenesis
Improves renal function	↓ Serum creatinine and BUN; improved tubular structure and histological integrity

Abbreviations: BUN, blood urea nitrogen; IL, interleukin; HMGB1, high mobility group box 1; TNF-α, tumor necrosis factor alpha.

In conclusion, IL-37 serves as a critical modulator of the inflammatory and immune responses implicated in AKI. Its multifaceted mechanisms, including suppression of pro-inflammatory signaling, reduction of oxidative stress, modulation of immune cell behavior, and support of vascular integrity, position it as a promising therapeutic candidate.

IL-37 in diabetic kidney disease (DKD). Recent evidence indicates that IL-37 plays a protective role in DKD through multiple molecular and cellular mechanisms. Its expression is markedly reduced in the serum and kidney tissues of patients with DKD [**16, 18**]. This downregulation correlates strongly with markers of disease severity, including increased proteinuria, elevated serum creatinine, reduced estimated glomerular filtration rate (eGFR), and more extensive interstitial fibrosis [**16, 18**]. One of the key protective mechanisms of IL-37 in DKD involves the inhibition of renal fibrosis. In diabetic mouse models, both transgenic overexpression and treatment with recombinant IL-37 significantly attenuate fibrotic remodeling [**16**]. IL-37 achieves this by restoring fatty acid oxidation (FAO) in tubular epithelial cells, primarily through upregulation of carnitine palmitoyl-transferase 1A (CPT1A), an essential enzyme in FAO. Improved FAO prevents lipid accumulation in renal tissues, thereby reducing the activation of fibrotic pathways [16]. Transgenic DKD mice expressing human IL-37 exhibit lower levels of proteinuria, serum creatinine, and blood urea nitrogen, alongside reduced expression of tubular injury markers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) [**16**].

Furthermore, IL-37 exerts potent anti-inflammatory and anti-oxidative effects in the diabetic kidney. It downregulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, while also suppressing MDA [**18**]. Simultaneously, it enhances the activity of protective molecules including superoxide dismutase (SOD) and Bcl-2, thereby limiting apoptosis in podocytes and tubular epithelial cells [**18**]. In addition to these effects, IL-37 has been shown to inhibit the STAT3–cyclophilin A (CypA) signaling pathway in podocytes, which is activated under hyperglycemic conditions and contributes to inflammatory and oxidative damage [**18**]. These multifaceted actions of IL-37 in DKD are summarized in Table 3.

Table 3

IL-37 mechanisms of action in diabetic kidney disease

Mechanism	Effect in DKD
Reduced expression in DKD	Correlates with ↑ fibrosis, ↑ serum creatinine, ↑ proteinuria, ↓ eGFR
Anti-fibrotic activity	Restores FAO via ↑ CPT1A; ↓ lipid accumulation and fibrotic signaling
Improvement of renal function	↓ Proteinuria, ↓ serum creatinine, ↓ BUN, ↓ KIM-1, ↓ NGAL
Anti-inflammatory and antioxidant roles	↓ TNF-α, IL-1β, IL-6, MDA; ↑ SOD, Bcl-2; ↓ apoptosis in renal cells
Inhibition of STAT3–CypA signaling	Prevents high glucose-induced podocyte injury

Abbreviations: Bcl-2 – B-cell lymphoma; BUN, blood urea nitrogen; CPT1A, carnitine palmitoyltransferase 1A; CypA, cyclophilin A; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FAO, fatty acid oxidation; IL, interleukin; KIM-1, kidney injury molecule-1; MDA, malondialdehyde; NGAL, neutrophil gelatinase-associated lipocalin; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor alpha.

In summary, IL-37 is significantly downregulated in DKD, and its restoration confers protection against inflammation, oxidative stress, fibrosis, and functional deterioration.

IL-37 in autosomal dominant polycystic kidney disease (ADPKD). Experimental models of ADPKD have demonstrated that transgenic expression of human IL-37b significantly suppresses cyst development in the collecting ducts [19]. This protective effect is observed in both early-onset and adult-onset forms of the disease. Furthermore, exogenous administration of recombinant IL-37b also reduces cyst burden in early-stage models, suggesting that IL-37 may be effective both prophylactically and therapeutically. Mechanistically, IL-37b mediates its effects through the modulation of innate immune signaling pathways. Specifically, IL-37b enhances type I interferon responses in kidney-resident macrophages [19]. Activation of this pathway leads to suppression of cyst initiation and limits cyst expansion. Importantly, the therapeutic effect of IL-37b is abrogated when type I interferon signaling is blocked, confirming the central role of this pathway in mediating IL-37's action. Interestingly, the reduction in cyst formation is not associated with a decrease in the total number of macrophages within the kidney. Instead, IL-37b appears to reprogram macrophage function toward a protective, anti-cytogenic phenotype, rather than reducing macrophage infiltration or presence. This functional modulation underscores the precision of IL-37's immunoregulatory effects in the renal microenvironment. These findings suggest that IL-37 represents a promising immunotherapeutic candidate for ADPKD. The main mechanisms by which IL-37 exerts its effects in ADPKD are summarized in Table 4

Table 4

IL-37 mechanisms of action in polycystic kidney disease

Mechanism	Effect in ADPKD models
Suppression of cyst initiation	↓ Cyst burden in collecting ducts (early- and adult-onset disease)
Activation of type I interferon signaling	↑ IFN response in renal macrophages; essential for anti-cyst effect
Functional reprogramming of macrophages	No change in macrophage numbers; shift toward anti-cystogenic phenotype
Therapeutic impact	↓ Cyst growth with transgenic or recombinant IL-37b; potential therapeutic use

Abbreviations: IFN, interferon; IL, interleukin.

Therapeutic applications and delivery strategies. Although IL-37's contribution has been well-documented in preclinical models of kidney disease, the translation of these findings into viable therapeutic interventions requires the development of effective delivery strategies and rigorous validation in clinical settings.

Recombinant IL-37 protein therapy. As discussed above, the administration of recombinant human IL-37 (rhIL-37) has demonstrated therapeutic benefits in experimental nephropathies. For example, in diabetic kidney disease (DKD) models, rhIL-37 reduces inflammatory cytokines (such as TNF-α, IL-6, and IL-1β), mitigates oxidative stress, and improves renal function, including reductions in proteinuria and renal fibrosis [16]. However, protein-based therapies face challenges including short half-life, limited tissue penetration, potential immunogenicity, and the need for repeated administration [20]. Optimization of protein stability and formulation will be key for clinical viability.

Gene therapy approaches. Gene delivery methods, such as plasmid or viral vector-mediated transfection, enable sustained expression of IL-37 in target tissues. Transgenic mouse models expressing human IL-37 have been instrumental in demonstrating long-term protective effects, particularly in models of AKI, CKD, and DKD [16, 19]. AAV (adeno-associated virus)-based vectors targeting renal parenchyma represent a promising avenue for organ-specific gene therapy, although safety, dose control, and regulatory barriers remain significant hurdles [8].

Cell-based and nanocarrier delivery systems. Emerging strategies leverage cell-derived vesicles and nanoparticles for targeted IL-37 delivery. Neutrophil-derived nanovesicles loaded with IL-37 have shown efficacy in localizing treatment to injured renal endothelial cells, reducing inflammation and preserving microvascular integrity during ischemia-reperfusion injury [17]. Similarly, liposome or polymer-based nanoparticles may enhance delivery specificity and protect IL-37 from degradation in circulation [21].

Combination therapies. IL-37's broad anti-inflammatory effects suggest potential synergy with existing therapies. Co-administration with immunosuppressants (corticosteroids, calcineurin inhibitors), antifibrotic agents (pirfenidone, ACE inhibitors), or metabolic modulators (SGLT2 inhibitors) may enhance therapeutic outcomes in multifactorial kidney diseases such as DKD or lupus nephritis [10, 15, 22]. However, such approaches warrant systematic evaluation in controlled studies.

Challenges and clinical translation. Key translational obstacles include defining optimal therapeutic windows, establishing dosing regimens, and monitoring potential off-target effects, particularly given IL-37's broad immunosuppressive capabilities [8, 10]. Importantly, isoform-specific functions and tissue distribu-

tion may influence treatment outcomes and need to be considered in therapy design.

Diagnostic and biomarker potential of IL-37 in kidney disease. IL-37 has emerged not only as a cytokine with therapeutic relevance but also as a potential biomarker reflecting disease severity and inflammatory activity in various kidney disorders. Its expression patterns in both circulating blood and renal tissue correlate with pathological features of kidney injury, offering potential diagnostic and prognostic utility. In AKI, elevated IL-37 levels correspond with reduced inflammation and oxidative stress [14, 17]. Similarly, in DKD, serum and renal IL-37 levels are significantly reduced, with lower expression strongly associated with increased proteinuria, elevated serum creatinine, reduced eGFR, and greater interstitial fibrosis [16]. In contrast, clinical studies focusing on broader CKD populations have reported a different pattern. Li et al investigated plasma IL-37 levels in patients with CKD and nephrotic syndrome (NS) compared to healthy controls [23]. The researchers enrolled 57 CKD patients, 13 NS patients, and 22 healthy individuals, further stratifying the CKD group by disease stage (stages 1, 3, and 5). Using ELISA, they found that plasma IL-37 levels were significantly higher in both CKD and NS patients than in healthy controls. Interestingly, IL-37 levels did not differ significantly among the different CKD stages, suggesting that its elevation is a general feature of CKD rather than stage-specific. After treatment, IL-37 levels decreased in both CKD and NS groups, and in CKD patients, IL-37 levels positively correlated with white blood cell and lymphocyte counts [23]. In line with these findings, another observational study found that serum IL-37 levels were significantly higher in patients undergoing hemodialysis (HD), especially in those with subclinical or overt hypothyroidism, compared to healthy controls [24]. In addition, IL-37 levels have been shown to be significantly elevated in patients with systemic lupus erythematosus compared to healthy controls and were correlated with high disease activity, mucocutaneous involvement, and renal involvement [22].

These findings suggest that elevated plasma IL-37 may serve as an auxiliary diagnostic marker for CKD, potentially reflecting an ongoing inflammatory or immune response. Because IL-37 levels inversely correlate with pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), particularly in cardiovascular diseases [25], measuring IL-37 alongside traditional markers may improve diagnostic accuracy. Specifically, a combined cytokine profile (high IL-6/IL-1β and low IL-37) may better distinguish inflammatory from non-inflammatory conditions, addressing the limitations of current markers in clinical practice [26, 27].

Limitations and future directions. Despite compelling preclinical evidence supporting the anti-inflammatory and tissue-protective functions of IL-37 in kidney diseases, several important limitations must be addressed before translating these findings into clinical applications. One of the fundamental biological challenges lies in the species-specific nature of IL-37. Mice, commonly used in preclinical research, lack an endogenous IL-37 gene, necessitating the use of human IL-37 transgenic models or recombinant protein administration [16, 19]. While informative, these approaches do not fully recapitulate the endogenous regulation, isoform dynamics, or receptor interactions that might occur in humans. Furthermore, the distinct roles of IL-37 isoforms (a–e), including their tissue-specific expression and functional relevance in renal physiology and pathology, remain poorly understood [12, 13].

From a therapeutic development perspective, optimal dosing strategies, routes of administration, and pharmacokinetic profiles for IL-37-based therapies are not yet established. Most available data stem from short-term animal studies, and there is limited insight into the long-term safety of exogenous IL-37, particularly regarding its immunosuppressive capacity and potential to interfere with host defense mechanisms [10, 12]. The development of targeted delivery platforms, such as nanoparticle systems or gene therapy vectors, offers promise but also introduces additional regulatory and safety considerations.

Emerging applications of IL-37 in clinical nephrology offer exciting but as yet untested possibilities. For instance, chronic inflammation is a key contributor to adverse outcomes in patients undergoing peritoneal dialysis (PD) or HD. Peritoneal inflammation and fibrosis are major complications in PD, often driven by recurrent peritonitis and exposure to bioincompatible dialysis fluids, leading to increased levels of inflammatory cytokines such as IL-1β and IL-6, and activation of profibrotic pathways such as TGF-β1 [28, 29]. Given IL-37's broad anti-inflammatory and anti-fibrotic properties, suppression of pro-inflammatory cytokines, inhibition of immune cell activation, and attenuation of fibrosis in various tissues-it is plausible that IL-37 could counteract the inflammatory and fibrotic processes in the peritoneum. Although direct studies in PD are lacking, the mechanistic rationale is strong, and IL-37's efficacy in other models of tissue fibrosis and inflammation supports this hypothesis. However, the findings that IL-37 is already elevated in the HD population complicate the rationale for further enhancing its activity [24]. The increased IL-37 may represent the body's attempt to counteract ongoing inflammation, but it may be insufficient to fully control the inflammatory burden, or it may indicate a state of cytokine resistance or immune dysregulation. Rather than simply increasing IL-37 levels, strategies may need to focus on enhancing its functional activity or overcoming possible resistance mechanisms. Additionally, the immunosuppressive effects of IL-37 raise concerns about infection risk in an already immunocompromised population.

To advance IL-37 toward clinical utility, several key research priorities should be addressed. First, early-phase clinical trials are needed to evaluate safety, tolerability, and pharmacodynamics in both acute and chronic kidney disease populations. Second, the devel-

opment of isoform-specific recombinant proteins or gene constructs will facilitate more precise therapeutic strategies. Third, IL-37 should be explored not only as a therapeutic agent but also as a biomarker for inflammation, fibrosis, and disease progression. Finally, combination approaches integrating IL-37 with existing immunosuppressants, antifibrotics, or metabolic agents may offer synergistic benefits and should be explored in preclinical models and trial settings.

Conclusions. The review provides an updated perspective on the immunobiological functions and potential clinical applications of IL-37, with a particular focus on its relevance to kidney disease. IL-37 is recognized for its broad immunomodulatory roles, including suppression of inflammatory responses, anti-tumor activity, and enhancement of antimicrobial defenses. These properties have positioned IL-37 as a promising candidate in emerging cytokine-based immunotherapeutic strategies. Although its functions have been explored across a wide spectrum of pathological conditions, growing evidence highlights its relevance in renal pathophysiology, including AKI, CKD, DKD, and ADPKD. The pleiotropic actions of IL-37, mediated through its interaction with IL-18 receptor α and SIGIRR/IL-1R8, suggest its potential utility not only in modulating kidney inflammation and fibrosis but also as a target for immune gene therapy. Thus, IL-37 represents a compelling immunotherapeutic molecule with promising diagnostic and therapeutic applications in a range of kidney diseases.

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References:

1. *Luyckx VA, Tonelli M, Stanifer JW.* The global burden of kidney disease and the sustainable development goals. Bull World Health Organ. 2018;96(6):414-422D. doi: 10.2471/BLT.17.206441.
2. *Joumaa JP, Raffoul A, Sarkis C, Chatrieh E, Zaidan S, Attieh P, et al.* Mechanisms, Biomarkers, and Treatment Approaches for Diabetic Kidney Disease: Current Insights and Future Perspectives. J Clin Med. 2025;14(3):727. doi: 10.3390/JCM14030727.
3. *Frąk W, Kućmierz J, Szlagor M, Młynarska E, Rysz J, Franczyk B.* New Insights into Molecular Mechanisms of Chronic Kidney Disease. Biomedicines. 2022; 10(11):2846. doi: 10.3390/BIOMEDICINES10112846.
4. *Stenvinkel P, Chertow GM, Devarajan P, Levin A, Andreoli SP, Bangalore S, Warady BA.* Chronic Inflammation in Chronic Kidney Disease Progression: Role of Nrf2. Kidney Int Rep. 2021;6(7):1775-87. doi: 10.1016/j.ekir.2021.04.023.
5. *Rispoli RM, Popolo A, De Fabrizio V, d'Emmanuele di Villa Bianca R, Autore G, Dalli J, et al.* Targeting Inflammatory Imbalance in Chronic Kidney Disease: Focus on Anti-Inflammatory and Resolution Mediators. Int J Mol Sci. 2025;26(7):3072. doi: 10.3390/IJMS26073072.
6. *Barkas F, Sener YZ, Golforoush PA, Kheirkhah A, Rodriguez-Sanchez E, Novak J, et al.* Advancements in Risk Stratification and Management Strategies in Primary Cardiovascular Prevention. Atherosclerosis. 2024;395:117579. doi: 10.1016/j.atherosclerosis.2024.117579.
7. *Popov SV, Melekhovets OK, Demikhova NV, Vynnychenko LB, Khil'ko IeS, Tychyna DO, Murga IV.* Application of "reytoil" in prevention of atherosclerosis in diabetes patients. Lik Sprava. 2012;(8):119-26. [In Ukrainian].
8. *Su Z, Tao X.* Current Understanding of IL-37 in Human Health and Disease. Front Immunol. 2021;12:696605. doi: 10.3389/fimmu.2021.696605/xml/nlm.
9. *Gu M, Jin Y, Gao X, Xia W, Xu T, Pan S.* Novel Insights into IL-37: An Anti-Inflammatory Cytokine with Emerging Roles in Anti-Cancer Process. Front Immunol. 2023;14:1278521. doi: 10.3389/fimmu.2023.1278521.
10. *Wang L, Quan Y, Yue Y, Heng X, Che F.* Interleukin-37: A crucial cytokine with multiple roles in disease and potentially clinical therapy. Oncol Lett. 2018;15(4):4711-19. doi: 10.3892/ol.2018.7982.
11. *Yan J, Zhang Y, Cheng S, Kang B, Peng J, Zhang X, et al.* Common genetic heterogeneity of human interleukin-37 leads to functional variance. Cell Mol Immunol. 2017;14(9):783-91. doi: 10.1038/cmi.2016.48.
12. *Jia H, Liu J, Han B.* Reviews of Interleukin-37: Functions, Receptors, and Roles in Diseases. Biomed Res Int.2018;2018:3058640. doi: 10.1155/2018/3058640.
13. *Quirk S, Agrawal DK.* Immunobiology of IL-37: mechanism of action and clinical perspectives. Expert Rev Clin Immunol. 2014;10(12):1703-9. doi: 10.1586/1744666X.2014.971014.
14. *Pinto PE, Requião-Moura AM, Ritchie FD.* IL-37 Expression Improves Renal Function after Ischemia and Reperfusion in Mce Model. American Journal of BioMedicine. 2021;9(4):207–24. doi: 10.18081/2333-5106/9.4/224.

15. *Zeng H, Zhou K, Ye Z.* Biology of interleukin-37 and its role in autoimmune diseases (Review). Exp Ther Med. 2022;24(2):495. doi: 10.3892/etm.2022.11422.
16. *Xiong L, He T, Liu C, Qin S, Xiao T, Xin W, et al.* IL-37 Ameliorates Renal Fibrosis by Restoring CPT1A-Mediated Fatty Acid Oxidation in Diabetic Kidney Disease. Kidney Dis (Basel). 2023;9(2):104-17. doi: 10.1159/000529460.
17. *Ma W, Wu D, Long C, Liu J, Xu L, Zhou L, et al.* Neutrophil-Derived Nanovesicles Deliver IL-37 to Mitigate Renal Ischemia-Reperfusion Injury via Endothelial Cell Targeting. J Control Release. 2024;370:66-81. doi: 10.1016/j.jconrel.2024.04.025.
18. *Zhang X, Zhu Y, Zhou Y, Fei B.* Interleukin 37 (IL-37) Reduces High Glucose-Induced Inflammation, Oxidative Stress, and Apoptosis of Podocytes by Inhibiting the STAT3–Cyclophilin A (CypA) Signaling Pathway. Med Sci Monit. 2020;26:e922979. doi: 10.12659/MSM.922979.
19. *Zylberberg AK, Cottle DL, Runting J, Rodrigues G, Tham MS, Jones LK, et al.* Modulating Inflammation with Interleukin 37 Treatment Ameliorates Murine Autosomal Dominant Polycystic Kidney Disease. Kidney Int. 2024;105(4):731-43. doi: 10.1016/j.kint.2023.12.006.
20. *Bujotzek A, Tiefenthaler G, Lariviere L, D'Andrea L, Marquez EA, Rudloff I, et al.* Protein Engineering of a Stable and Potent Anti-Inflammatory IL-37-Fc Fusion with Enhanced Therapeutic Potential. Cell Chem Biol. 2022;29(4):586-96.e4. doi: 10.1016/j.chembiol.2021.10.004.
21. *Shang S, Li X, Wang H, Zhou Y, Pang K, Li P, et al.* Targeted therapy of kidney disease with nanoparticle drug delivery materials. Bioact Mater. 2024;37:206-21. doi: 10.1016/j.bioactmat.2024.03.014.
22. *Tawfik MG, Nasef SI, Omar HH, Ghaly MS.* Serum Interleukin-37: A New Player in Lupus Nephritis? Int J Rheum Dis. 2017;20(8):996-1001. doi: 10.1111/1756-185X.13122.
23. *Li C, Zhang J, Zhu K, Xu J.* Expression and Clinical Significance of Interleukins-37 in Patients with Chronic Kidney Disease. International Journal of Laboratory Medicine. [Internet].2017;38(21):2947–49. Available from: http://wprim.whocc.org.cn/admin/article/articleDetail?WPRIMID=667222&articleId=667222&locale=en_US.
24. *Faris ST, Al-Fartosy AJM, Al-Fregi AA.* Interleukin-37 and Interleukin-18 as Prognostic Biomarkers for End-Stage Renal Disease. Azerbaijan Medical Journal. [Internet]. 2022;62(4):1429-39. Available from: https://faculty.uobasrah.edu.iq/uploads/publications/1656511527.pdf.
25. *Rafiei A, Ahmadi R, Kazemian S, Rahimzadeh-Fallah T, Mohammad-Rezaei M, Azadegan-Dehkordi F, et al.* Serum levels of IL-37 and correlation with inflammatory cytokines and clinical outcomes in patients with coronary artery disease. J Investig Med. 2022;70(8):1720-27. doi: 10.1136/jim-2021-002134.
26. *Gaïseniuk FZ, Driianskaia VE, Drannik GN, Rudenko MIu, Lavrenchuk OV, Stepanova NM, et al.* Proinflammatory cytokines in patients with pyelonephritis. Lik Sprava. 2013;(6):32-37. [In Russian].
27. *Luxton R, Kiely J, Drake M.* Interleukins in Urine and Blood as Markers of Infection and as Risk Factors for Systemic Conditions. Eur Urol Focus. 2024;10(5):706-709. doi: 10.1016/j.euf.2024.09.016.
28. *Stepanova N.* The Gut-Peritoneum Axis in Peritoneal Dialysis and Peritoneal Fibrosis. Kidney Med. 2023;5(6):100645. doi: 10.1016/j.xkme.2023.100645.
29. *Ito Y, Sun T, Tawada M, Kinashi H, Yamaguchi M, Katsuno T, et al.* Pathophysiological Mechanisms of Peritoneal Fibrosis and Peritoneal Membrane Dysfunction in Peritoneal Dialysis. Int J Mol Sci. 2024;25(16):8607. doi: 10.3390/ijms25168607.