Review

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Interleukins in Urological Diseases

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Interleukins (ILs) are a group of cytokines that regulate immune responses and inflammation, playing important roles in the pathogenesis, diagnosis, and treatment of urological diseases. This review provides an analysis of the involvement of interleukins in bladder cancer, benign prostatic hyperplasia (BPH), renal cell carcinoma (RCC), urinary tract infections (UTIs), interstitial cystitis/bladder pain syndrome (IC/BPS), and urolithiasis. ILs regulate immune cell activity and mediate tumor progression, immune evasion, and inflammation, making them valuable biomarkers and therapeutic targets. Elevated levels of IL-6, IL-8, and IL-18 are associated with disease severity and prognosis in bladder cancer, RCC, and BPH. Additionally, IL-10 is anti-inflammatory, offering therapeutic potential in chronic inflammatory conditions such as BPH and IC/BPS. Emerging therapies targeting IL pathways, including IL-2 and IL-17 inhibitors, have shown promise in modulating immune responses and improving clinical outcomes. The diagnostic utility of urinary IL biomarkers, particularly IL-6 and IL-8, has been demonstrated in UTIs and urolithiasis. This review highlights not only the therapeutic potential of interleukins but also their integral role in the immunopathology of urological diseases, distinguishing it from previous analyses by emphasizing IL-targeted therapies to improve diagnostic and therapeutic outcomes.

Keywords: interleukins; urological dissease; prostate cancer; bladder cancer; urinary tract infection; urolithiasis; benign prostate hyperplasia

Introduction

Interleukins (ILs) are a group of cytokines that play critical roles in the immune system by promoting or inhibiting inflammation and interactions between cells, including T cells, B cells, and macrophages. Interleukins are classified into pro-inflammatory (e.g., IL-1, IL-6, IL-17) and anti-inflammatory (e.g., IL-10, IL-35) subtypes, each with specific biological functions [1,2]. These molecules bind to cell surface receptors, triggering intracellular signaling cascades that influence gene expression, proliferation, and apoptosis.

Interleukins have gained attention in urological diseases as diagnostic biomarkers, prognostic indicators, and therapeutic targets. Inflammatory responses mediated by interleukins are involved in conditions such as bladder cancer, urinary tract infections (UTIs), benign prostatic hyperplasia (BPH), and kidney diseases [3]. For instance, elevated levels of IL-17A and IL-23 have been identified in patients with bladder cancer and other urological disorders, suggesting their role in cancer development and inflammation [3,4].

Urinary biomarkers, such as IL-6 and IL-8, have demonstrated potential in predicting responses to therapies like Bacillus Calmette-Guérin (BCG) in non-muscle invasive bladder cancer (NMIBC), helping to guide treatment decisions [5]. Moreover, IL-18 has been shown to be an effective biomarker for acute kidney injury (AKI) and its severity, with higher sensitivity in pediatric patients [6].

In chronic kidney disease (CKD), increased levels of IL-6 and IL-8 are associated with inflammation and fibrosis, demonstrating their critical role in diagnosis and prognosis [7]. Furthermore, IL-10, an anti-inflammatory cytokine, can reduce inflammation in urological diseases and can be used as a target for treatment [8].

Interleukin pathways also contribute to autoimmune-related urological conditions, such as interstitial cystitis and glomerulonephritis. IL-6 has been identified as a key mediator of immune dysregulation, causing inflammation, tissue damage, and fibrosis [9]. Studies on IL-17 highlight its role in modulating immune responses and sustaining chronic inflammation in autoimmune urological disorders [10].

This review aims to evaluate the role of interleukins in urological diseases, focusing on their diagnostic, prognostic, and therapeutic implications. We aim to advance our understanding and improve clinical outcomes in urological medicine by explaining the molecular mechanisms underlying interleukin-mediated pathways. In this process, we thoroughly reviewed the latest literature to ensure the development of a scientifically comprehensive and up-to-date review.

Interleukins in Bladder Cancer

Bladder cancer is one of the most common urological cancers, with urothelial carcinoma being its most common subtype. Recent studies emphasize the crucial role of cytokines, particularly interleukins, in bladder cancer pathogenesis, progression, and prognosis. These molecules mediate inflammation, immune responses, and interactions within the tumor microenvironment (TME). Based on current research, specific interleukins, including IL-6, IL-8, IL-1, and IL-15, play significant roles in bladder cancer [11].

IL-6 and IL-8 are among the most studied cytokines in bladder cancer. Elevated levels of IL-6 and IL-8 in urine have shown strong correlations with the presence and severity of bladder urothelial carcinoma. A pilot study demonstrated that combining IL-6 and IL-8 in urine samples could distinguish high-grade urothelial carcinoma from benign conditions, with a sensitivity of 90% and specificity of 81.25% [11]. In the study by Kumari *et al.* (2017) [12], serum IL-6 levels were found to be significantly associated with invasion in bladder cancer patients ($p < 0.01$), while urinary IL-8 levels showed a strong correlation with tumor recurrence ($p < 0.05$). These findings show their potential as non-invasive biomarkers for early diagnosis and monitoring. Moreover, IL-8 plays an important role in the TME by recruiting immune cells such as neutrophils and monocytes, which differentiate into tumor-associated macrophages (TAMs) and polarize into the M2 phenotype. These M2 macrophages support tumor progression through angiogenesis, immune suppression, and tissue remodeling. Functionally, c-Fos is a mediator, linking hepatocyte growth factor (HGF) signaling to increased IL-8 transcription in bladder cancer cells, establishing a positive feedback loop that amplifies neutrophil recruitment and inflammation (Fig. 1). Clinically, urine IL-8 is a more reliable biomarker than serum IL-8 for predicting bladder cancer prognosis and response to immune checkpoint blockade (ICB). That shows its importance as both a diagnostic tool and a therapeutic target in cancer treatment [13,14].

IL-1 and its receptor antagonist (IL-1RA) are involved in inflammation and tumor progression. Elevated IL-1β expression has been linked to vascular and lymphatic invasion in invasive bladder cancer, correlating with higher tumor grades and poor survival outcomes [15]. Conversely, IL-1RA acts as an anti-inflammatory molecule that inhibits IL-1 activity. Reduced IL-1RA expression has been associated with increased invasiveness and migration of bladder cancer cells [16].

IL-15 has emerged as a promising cytokine in bladder cancer immunotherapy. IL-15's role in enhancing the efficacy of BCG therapy in bladder cancer is well-supported by its ability to stimulate innate and adaptive immune responses. Specifically, IL-15 promotes the proliferation and activation of natural killer (NK) cells and CD8+ T cells via the CD122/CD132 receptor complex. This mechanism supports its synergistic effect with BCG, as demonstrated in a Phase 1b clinical trial where intravesical administration of an IL-15 superagonist (N-803) alongside BCG led to significant increases in infiltrating NK and CD8+ T cells within the bladder TME. Impressively, all nine patients in the trial remained disease-free during a six-year follow-up, highlighting the potential of IL-15 to improve tumor clearance and reduce recurrence rates in NMIBC [17]. Furthermore, inflammatory markers and cytokines, such as IL-6 and IL-8, have also shown prognostic value in metastatic urothelial carcinoma. Lower IL-6 and IL-8 levels correlate with better response rates and survival in patients undergoing immunotherapy with avelumab [18].

Interleukins in Interstitial Cystitis/Bladder Pain Syndrome

In interstitial cystitis/bladder pain syndrome (IC/BPS), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1β (IL-1β), and interleukin-17 (IL-17) are key contributors to chronic inflammation and urothelial epithelial damage (Table 1, Ref. [19–25]). IL-6 activates the Janus Kinase/Signal Transducer and Activator of Transcription 3 (JAK/STAT3) pathway, promoting the transcription of pro-inflammatory genes, disrupting urothelial cell junctions, and enhancing nociceptive sensitization via JAK/Phosphoinositide 3-Kinase (PI3K)/Transient Receptor Potential Vanilloid 1 (TRPV1) signaling [19–21]. Simultaneously, IL-8 recruits and activates mast cells, releasing histamine, proteases, and matrix metalloproteinases (MMPs), which amplify inflammation and degrade the extracellular matrix [19–21]. IL-1β plays a central role in inducing and perpetuating inflammation by activating the inflammasome and promoting the differentiation of T-helper 17 (Th17) cells, which release IL-17 to drive chronic inflammation and tissue damage further [22]. IL-17, primarily secreted by Th17 cells, contributes to the recruitment of neutrophils and the amplification of the inflammatory response, as well as enhancing tissue remodeling and fibrosis through pathways like nuclear factor kappa-B (NF-κB) and IL-17RA signaling [23]. These cytokines disrupt the urothelial barrier, marked by reduced expression of proteins such as E-cadherin and uroplakin III. This leads to increased bladder epithelial permeability, chronic pain, and urinary urgency. Elevated levels of IL-6, IL-8, IL-1β, and IL-17 correlate with symptom severity and highlight their pivotal roles in the pathogenesis of IC/BPS [19–23].

Conversely, IL-10 plays a protective anti-inflammatory role by inhibiting the expression of pro-inflammatory cytokines such as IL-6 and IL-1β (Table 1). It modulates immune responses and promotes tissue repair by reducing oxidative stress and modulating the JAK/STAT signaling pathway [24]. IL-10 has been

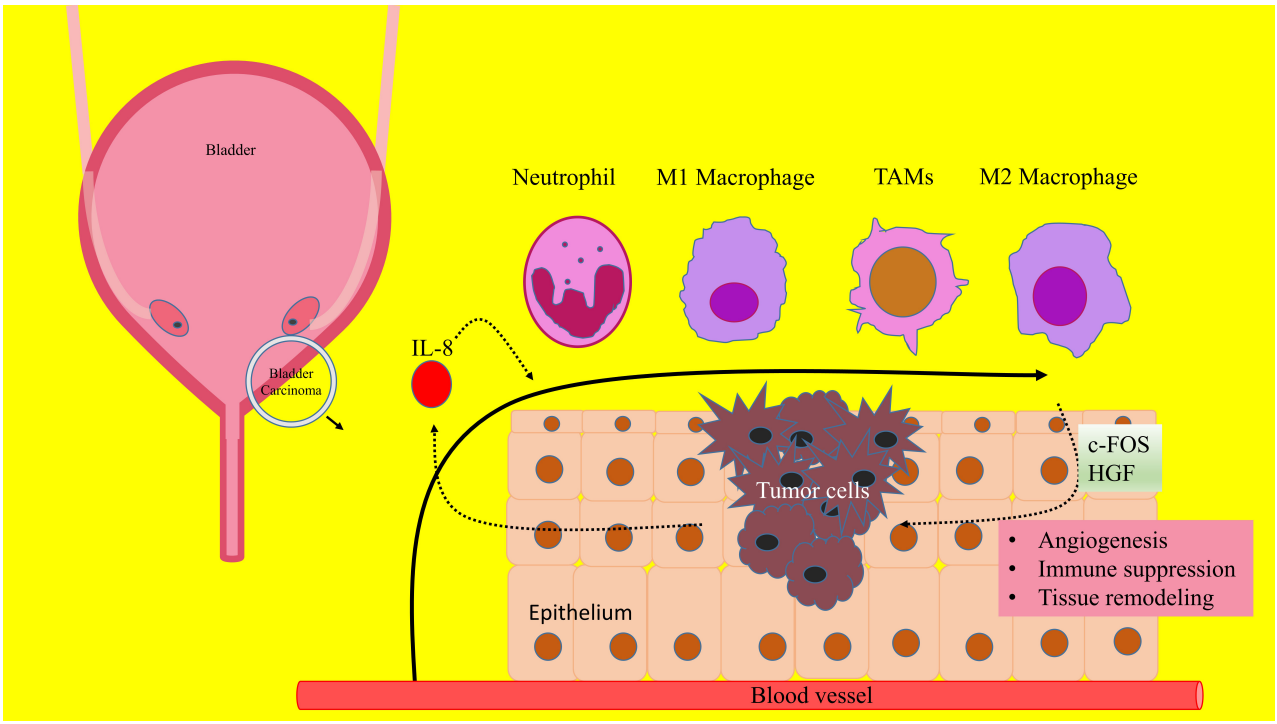

Fig. 1. Role of interleukin (IL)-8 and M2 macrophage in bladder carcinoma. The figure illustrates the role of IL-8 in the tumor microenvironment (TME) of bladder carcinoma, emphasizing its function in recruiting neutrophils and monocytes, which differentiate into tumor-associated macrophages (TAMs) and polarize into the M2 phenotype. These M2 macrophages facilitate tumor progression through angiogenesis, immune suppression, and tissue remodeling. Additionally, the diagram highlights the interaction between c-Fos and hepatocyte growth factor (HGF) in bladder cancer cells, which enhances IL-8 transcription, establishing a positive feedback loop that amplifies neutrophil infiltration and inflammation. The figure was created by authors with PowerPoint 2016, Microsoft, Redmond, WA, USA.

shown to decrease inflammatory markers and alleviate detrusor fibrosis in experimental models, making it a potential therapeutic target for IC/BPS [24]. However, drugs targeting IL-10 have limited clinical use due to their systemic immunosuppressive side effects, which increase susceptibility to infections and limit broader use. Current research focuses on enhancing IL-10's stability and localized effects, such as through recombinant IL-10 delivery or encapsulated IL-10 nanoparticles [25]. In preclinical studies, these new treatment strategies promise to balance IL-10's anti-inflammatory effects by reducing inflammation and cytokines while minimizing systemic risks [25]. These interleukins and their mechanisms are summarized in Table 1.

Interleukins in Benign Prostate Hyperplasia (BPH)

BPH is a non-malignant enlargement of the prostate gland, primarily affecting aging men. Chronic inflammation has been identified as a significant factor in the pathogenesis of BPH. Research, including findings from the REDUCE (REduction by DUtasteride of prostate Cancer Events) trial, suggests a correlation between prostatic inflammation and an increased risk of acute urinary retention in BPH patients. While the exact mechanisms between chronic inflammation and prostatic enlargement remain unclear, it is increasingly evident that inflammation contributes to the progression of bladder outlet obstruction (BOO) by exacerbating prostatic tissue changes [26–28]. Interleukins, a group of cytokines, play essential roles in modulating inflammation, cellular proliferation, and tissue remodeling within the prostate. Among these, IL-6 functions as a pro-inflammatory cytokine associated with cell proliferation, angiogenesis, and tissue remodeling. Elevated IL-6 levels have been correlated with increased prostate volume and more severe lower urinary tract symptoms (LUTS) in BPH patients while also promoting smooth muscle contraction. This contributes to BOO [29,30]. Similarly, IL-8 is a pro-inflammatory chemokine that enhances angiogenesis and cellular proliferation. While studies have not shown significant differences in IL-8 concentrations between BPH and control groups, IL-8 may still influence tissue remodeling and smooth muscle hypercontractility in BPH [30,31].

On the other hand, IL-10 serves as an anti-inflammatory cytokine that suppresses the immune system and inflammation. Genetic polymorphisms in IL-10 and

Table 1. Interleukins in interstitial cystitis/bladder pain syndrome (IC/BPS).

Interleukin	Role	Clinical importance	References
IL-6	Drives chronic inflammation and epithelial damage.	Associated with the severity of pain and other symptoms.	[19–21]
IL-8	Activates mast cells, releasing histamine and proteases.	Sustains inflammation, contributing to symptom persistence.	[19–21]
IL-17	Promotes chronic inflammation and fibrosis.	Emerging as a therapeutic target.	[22,23]
IL-10	Suppresses inflammation and promotes tissue repair.	Limited clinical use due to systemic immunosuppressive effects.	[24,25]

IL-6, interleukin-6; IL-8, interleukin-8; IL-17, interleukin-17; IL-10, interleukin-10.

its receptors (IL10RA and IL10RB) have been associated with variations in prostate size and Prostate-Specific Antigen (PSA) levels in BPH patients, highlighting their regulatory potential in mitigating chronic inflammation [32]. Recent studies have investigated the genetic basis of prostate size in BPH, focusing on the role of IL-10 polymorphism. Specifically, single nucleotide polymorphisms (SNPs) in the IL-10 promoter region, such as -1082A>G (rs1800896), have been examined for their role in BPH. One study found that variations in *IL-10* mRNA expression correlated with changes in prostate volume. Patients with larger prostate sizes have decreased levels of expression. Genetic studies suggest IL-10 promoter SNPs may not significantly affect BPH risk universally, indicating population-specific or multifactorial influences [33,34]. Additionally, interleukin-17 (IL-17), a pro-inflammatory cytokine, plays an important role in tissue remodeling and fibrosis, thereby promoting fibroblast growth and cytokine release, contributing to prostate enlargement [30]. Also, interleukin-18 (IL-18) is a pro-inflammatory cytokine that correlates with prostate volume and inflammation severity. Environmental and occupational exposures have been shown to modulate IL-18 levels, promoting inflammation and BPH progression [35]. IL-17 and IL-18 contribute to fibrosis and smooth muscle hypercontractility in BPH through distinct pro-inflammatory and fibrotic mechanisms. IL-17 induces fibrotic responses by enhancing extracellular matrix deposition, upregulating α-smooth muscle actin (α-SMA), and activating extracellular signal-regulated kinase (ERK) and Smad signaling pathways, which lead to increased fibronectin production [36]. Similarly, IL-18 promotes fibrosis by facilitating epithelial-mesenchymal transition (EMT) and increasing transforming growth factor-beta (TGF-β) signaling, leading to elevated collagen production. In addition, both cytokines stimulate inflammatory cascades, exacerbating tissue remodeling and contractility [37]. Therapeutically, targeting interleukin pathways represents a promising approach to BPH management. Current treatments, including alpha-blockers, 5-alpha reductase inhibitors, and anti-inflammatory agents, primarily alleviate symptoms without addressing inflammation at the molecular level [30]. Emerging therapies targeting specific cytokines, such as IL-6 and IL-17 inhibitors, are under investigation to reduce prostate inflammation and prevent disease progression. Anti-IL-6 and Anti-IL-17 targeted therapies have been studying in prostate cancer can be used in BPH because of similar effects of ILs in both tumoral cells and normal cells in prostate tissue but further studies are needed to use these treatments in BPH [38,39]. In summary, interleukins IL-6, IL-8, IL-10, IL-17, and IL-18 have roles in the development of BPH. Understanding the interactions and inflammatory pathways could provide improved treatment strategies for managing BPH.

Interleukins in Renal Cell Carcinoma (RCC)

RCC accounts for approximately 3% of all cancers and is the most prevalent form of kidney malignancy. Among its subtypes, clear-cell RCC (ccRCC) constitutes 80% of cases and is characterized by high metastatic potential and poor prognosis [40]. Given its often late-stage detection, immunotherapy has emerged as a vital treatment strategy [41]. Cytokines, particularly interleukins, play critical roles in modulating the tumor microenvironment and influencing the immune response against RCC.

IL-2 was the first Food and Drug Administration (FDA)-approved immunotherapy for RCC, demonstrating significant efficacy in metastatic cases. IL-2 promotes the expansion and differentiation of cytotoxic T cells and NK cells, enabling an anti-tumor immune response [42]. High-dose IL-2 therapy induces durable, complete responses in a subset of patients; however, its use is limited by severe toxicities, including vascular leak syndrome [42]. Advancements in IL-2 engineering have led to the development of modified IL-2 variants, such as polyethylene glycol-conjugated IL-2 (PEG-IL-2). PEG-IL-2 exhibits reduced binding to the IL-2α receptor subunit, thereby minimizing activation of regulatory T cells (Tregs) and systemic toxicities while maintaining its capacity to stimulate cytotoxic T cells and NK cells effectively [43,44].

Additionally, combining IL-2 with immune checkpoint inhibitors, such as anti-programmed death-1 (PD-1) therapies, has shown promise in enhancing anti-tumor activity. This combination works synergistically by stimulating T-cell proliferation via IL-2 while overcoming T-cell exhaustion mediated by checkpoint pathways, resulting in improved anti-tumor immune responses [45,46]. Clinical trials have demonstrated that the IL-2/anti-PD-1 combination significantly increases response rates and prolongs progression-free survival compared to monotherapies alone [46].

IL-4 and IL-13 are associated with Th2-mediated immune responses. Although their roles in RCC are less well-defined, IL-4 and IL-13 are implicated in tumor progression and immunosuppression. Both IL-4 and IL-13 have been shown to activate the Signal transducer and activator of transcription 6 (STAT6) signaling pathway, which promotes the expression of genes involved in cell proliferation and survival, as well as polarization of macrophages toward an M2 phenotype that supports tumor growth and suppresses anti-tumor immunity [47,48]. Elevated levels of IL-4 and IL-13 have been identified in the tumor microenvironment of various cancers, including RCC, correlating with poor prognosis [49].

In this context, dupilumab, a monoclonal antibody targeting IL-4 and IL-13 signaling via inhibition of the shared IL-4Rα receptor, has demonstrated potential in modulating tumor-induced immunosuppression. A single case study reported significant control of atopic dermatitis in a patient with metastatic RCC treated with dupilumab, with no signs of cancer progression over 20 months [50]. These findings suggest that targeting IL-4/IL-13 signaling may offer supportive therapeutic benefits in RCC. However, larger clinical studies and experimental data are necessary to confirm these observations and further elucidate the role of these cytokines in RCC pathogenesis.

IL-6 and IL-1β are pro-inflammatory cytokines involved in tumor growth, angiogenesis, and immune evasion. Studies have identified elevated levels of IL-6 and IL-1β in RCC, particularly in regressive tumor areas exhibiting wound-healing properties [51]. These cytokines have roles in both tumor progression and regression by activating fibroblasts and driving extracellular matrix remodeling: by targeting these pathways, it may be possible to achieve therapeutic benefits by reducing inflammation and boosting anti-tumor immunity. The heterogeneity of RCC necessitates combination therapies targeting multiple immune pathways. Synergistic approaches involving IL-2, immune checkpoint inhibitors, and cytokine modulators, such as IL-4/IL-13 inhibitors, show promise in overcoming resistance and improving patient outcomes [41,42]. Furthermore, novel IL-2 variants with enhanced selectivity and reduced toxicity are under investigation to maximize therapeutic efficacy [42]. Ongoing research is essential to elucidate the complex roles of interleukins in RCC and optimize their application in immunotherapy.

Interleukins in Urinary Tract Infection

UTIs are among the most common bacterial infections, affecting millions worldwide. Inflammatory cytokines, particularly interleukins, play a crucial role in the immune response to UTIs. This review summarizes current findings on the involvement of ILs, such as IL-6, IL-8, IL-10, IL-17, and IL-22, in the pathogenesis, diagnosis, and potential treatment strategies for UTIs [52–54].

IL-6 is a key pro-inflammatory cytokine involved in host defense during UTIs. It is rapidly secreted by uroepithelial cells upon bacterial infection, primarily mediated through Toll-like receptor (TLR) pathways [52]. IL-6 activates the STAT3 signaling pathway, promoting antimicrobial peptide production and limiting bacterial invasion [52]. Elevated urinary IL-6 levels have been correlated with UTI severity and progression to pyelonephritis [53]. For instance, an IL-6 threshold of $>$22.1 pg/mL has been shown to diagnose pyelonephritis with 50.0% sensitivity and 94.4% specificity [55].

IL-8 is a chemokine responsible for recruiting neutrophils to sites of infection. Increased urinary IL-8 levels are observed in acute pyelonephritis, indicating its role in neutrophil-mediated defense [56]. However, studies have shown that IL-8 levels alone cannot reliably differentiate between upper and lower UTIs [54]. Elevated IL-8 levels have also been linked to acute kidney injury associated with urosepsis [57]. High urinary IL-8 levels (mean urinary IL-8 level: 206.5 pg/mL for acute pyelonephritis) are highly predictive of active infection and offer a strong negative predictive value. Furthermore, a decrease in IL-8 levels following treatment indicates effective infection control [54].

IL-10 functions as an anti-inflammatory cytokine, balancing excessive immune responses to prevent tissue damage. Elevated IL-10 levels are associated with urosepsis, but their levels decrease significantly 24 hours after administering antibiotics. This cytokine likely contributes to the host's compensatory anti-inflammatory response [58].

IL-17 has been implicated in sex-specific immune responses to UTIs. Higher IL-17 expression in females promotes bacterial clearance, whereas males show suppressed IL-17 responses, leading to chronic infections. Recognizing these molecular differences highlights the importance of developing personalized diagnostic and treatment strategies for managing UTIs [59].

IL-22 is a cytokine with dual roles, including promoting epithelial repair and enhancing antimicrobial defenses. It may also modulate microbiota, affecting UTI susceptibility and progression [60].

Serum ILs have emerged as promising biomarkers for diagnosing UTIs and differentiating between upper and lower tract infections. For example, serum IL-6 and IL-8 have shown significant potential as biomarkers for acute pyelonephritis. As previously mentioned, urinary IL-8 increases in acute pyelonephritis but that cannot differentiate upper and lower UTIs [61]. Similarly, urinary IL-6 levels have demonstrated high sensitivity and specificity in predicting urosepsis following surgical procedures [53]. Moreover, the combined use of IL-8, Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Kidney Injury Molecule-1 (KIM-1) has been proposed for early diagnosis of acute kidney injury related to urosepsis [57].

Modulating IL pathways may offer new therapeutic strategies for UTIs. The modulation of IL pathways may

offer novel therapeutic strategies for UTIs. Targeting IL-6 and IL-22 pathways may enhance antimicrobial responses and tissue repair and reduce antibiotic dependence, while targeting IL-10 pathways may help control excessive inflammation and prevent tissue damage [52,58,60].

The latest therapeutic approaches to interleukins in UTIs have shifted toward immune response modulation with the purpose of controlling inflammation and enhancing host defenses. IL-6 inhibitors, such as tocilizumab, suppress extreme immune activation and subsequent tissue damage; thus, they hold promise in both acute and chronic UTI management [62]. IL-10 modulation has shown potential in preclinical models by promoting anti-inflammatory pathways via TLR5 signaling to prevent recurrent infections [63]. Targeting IL-17 pathways has effectively reduced bacterial persistence and tissue damage in chronic UTIs [64]. Crocetin and other natural compounds have proven their worth as natural supportive therapies due to their ability to lower IL-6 and IL-8, inhibit bacterial adhesion, and manage inflammation. Moreover, combining these compounds with antibiotics and interleukin inhibitors can give a decisive advantage by improving effectiveness and warfare to the urgent concern of antibiotic resistance [65].

Interleukins in Urolithiasis

Genetic, metabolic, and environmental factors influence urolithiasis, a multifactorial disease. Increasing evidence suggests that inflammation is important in stone formation and progression. Interleukins, a group of cytokines, are particularly implicated in inflammatory processes associated with urolithiasis [66,67].

Elevated urinary IL-6 levels have been observed in patients with urolithiasis, indicating its role in inflammation and immune modulation. The study has shown that IL-6 can mediate osteoclastogenesis and bone resorption, promoting calcium release and stone formation [68]. This process is closely linked to the Receptor Activator of Nuclear Factor Kappa-B Ligand/Receptor Activator of Nuclear Factor Kappa-B/Osteoprotegerin (RANKL/RANK/OPG) signaling pathway, which plays a pivotal role in the regulation of bone metabolism. IL-6 enhances the expression of RANKL, a critical factor in osteoclast differentiation and activity. RANKL binds to its receptor RANK on osteoclast precursors, initiating a cascade of signaling events that drive osteoclastogenesis and bone resorption. OPG, a decoy receptor for RANKL, counteracts this process by preventing RANKL-RANK interaction; however, elevated IL-6 levels can disrupt this balance by increasing RANKL expression and reducing the protective effect of OPG. This dysregulation may further exacerbate calcium release from bones, providing a substrate for urolithiasis formation [69–71].

Genetic polymorphisms and variations in cytokine genes, particularly IL-1β and IL-18, are key risk factors for urolithiasis. IL-1β, a pro-inflammatory cytokine, is associated with hypercalciuria and calcium oxalate stone formation, with genetic polymorphisms in IL-1β linked to increased urolithiasis risk [67,72–74]. However, there are mixed results from studies investigating IL-1β levels in patients. Some studies report elevated levels in urolithiasis cases, but in contrast, some studies report no significant differences compared to healthy controls [67,72,73]. That clarifies the need for further research to understand the role in stone formation. Similarly, IL-18 polymorphisms are strongly associated with calcium oxalate stones, potentially influencing inflammation and oxidative stress, thereby promoting stone formation [66,72]. Polymorphisms in IL-1 receptor antagonist (IL-1RN) genes have not consistently shown significant associations in all populations, suggesting that ethnic and environmental factors may play a role in urolithiasis susceptibility [75]. Additionally, IL-18 has been evaluated as a biomarker for renal injury during treatments like extracorporeal shock wave lithotripsy (ESWL), with studies showing that its levels remain stable post-procedure, suggesting its limited utility in detecting treatment-induced damage [72].

The relationship between interleukin levels and stone size in urolithiasis involves complex inflammatory and oxidative stress pathways. Larger stones are associated with an increased inflammatory response, as evidenced by elevated levels of cytokines like IL-2 and IL-8. IL-2, while typically reducing the risk of upper urinary tract stones through regulatory immune functions, is paradoxically elevated in cases of renal stone disease, suggesting a feedback mechanism where inflammation perpetuates stone growth [76]. Similarly, IL-8 significantly increases in areas with combined bladder and renal inflammation, correlating with the size and severity of the stones [77]. As stone size increases, oxidative stress rises, reflected in a shift in the thiol-disulfide balance toward disulfide dominance, which signals weakened antioxidant defenses and ongoing tissue damage [78]. This creates a harmful cycle where larger stones trigger more inflammation, oxidative stress, and immune system disruptions, which, in turn, cause further tissue damage and contribute to stone growth.

Elevated IL-8 levels have been identified in the urine of urolithiasis patients, suggesting its role as a chemotactic agent promoting leukocyte recruitment and inflammation. IL-8 will be used as a diagnostic biomarker in the future with new studies [76,77].

IL-2 has been shown to reduce the risk of renal stone formation, while its elevation may indicate inflammatory responses during stone progression [76].

Elevated levels of IL-7, IL-5, and other cytokines such as monokine induced by interferon-gamma (MIG)

Table 2. Comparison of IL-6 and IL-8.

Disease	Role of IL-6	Role of IL-8
Bladder cancer	Biomarker for severity and progression; promotes immune evasion and angiogenesis [11,12].	Recruits tumor-associated macrophages; linked to recurrence and immune checkpoint responses [13,14].
IC/BPS	Activates the JAK/STAT3 pathway, disrupting epithelial barriers [19–21].	Amplifies inflammation by recruiting mast cells [19–21].
BPH	Promotes inflammation, angiogenesis, and tissue remodeling [29,30].	Enhances angiogenesis and smooth muscle contraction [30,31].
RCC	Drives tumor growth and immune suppression [42].	Supports immune cell recruitment to the tumor microenvironment [51].
UTIs	Biomarker for infection severity; enhances antimicrobial defenses [52,53].	Chemotactic agent recruiting neutrophils [55,56].
Urolithiasis	Mediates inflammation and calcium metabolism disruptions [67,68,70].	Promotes leukocyte recruitment and inflammation [67,76].

BPH, benign prostatic hyperplasia; RCC, renal cell carcinoma; UTIs, urinary tract infections; JAK/STAT3, Janus Kinase/Signal Transducer and Activator of Transcription 3.

and macrophage inflammatory protein-1 alpha (MIP-1α) have been associated with inflammation and progression of lower urinary tract stones [76].

Anti-interleukin (anti-IL) therapies offer a promising approach to managing inflammation-related urolithiasis by targeting cytokines central to the inflammatory cascade. IL-1β is a key mediator in the inflammatory response associated with urolithiasis, and therapies like canakinumab (an IL-1β inhibitor) work by blocking its interaction with receptors, thereby reducing inflammation and associated tissue damage for the treatment of atherothrombosis. That may have potential future applications in urolithiasis [79]. IL-6 receptor antagonists, such as tocilizumab and clazakizumab, have the same potential with the IL-1β inhibitor in the treatment of urolithiasis [80]. Despite all these advancements, clinical studies remain limited. Future research will help solidify the role of anti-interleukin therapy in urinary stone disease; however, more clinical trials are needed to achieve this.

Discussion

Interleukins play an important role in immune modulation and inflammatory processes in tumor microenvironments in various urological diseases. Consolidated evidence supporting their diagnostic and therapeutic relevance has been reviewed in both the participation in pathophysiology and treatment strategies [12].

Interleukin pathway research should be directed at developing standardized detection protocols, validation of biomarkers, and new therapeutic approaches. Similarly, the measurement techniques for IL-6 and IL-8 in urine and serum should be robust and reproducible to ensure clinical reliability [9]. Multi-center studies are essential to confirm the diagnostic and prognostic lutility of these biomarkers across diverse populations. Advanced targeted therapies, such as nanoparticle-based IL-10 delivery systems, could provide localized effects while minimizing systemic side effects [25]. Investigating inhibitors for IL-17 and IL-18 may help manage fibrosis and chronic inflammation in conditions like BPH and urolithiasis [36]. Combination therapies, including IL-2 variants paired with immune checkpoint inhibitors, offer the potential for overcoming resistance and reducing toxicity in renal cell carcinoma [43].

Reviewed results point out that pathogenesis in bladder cancer involves significant participation of interleukins such as IL-6 and IL-8; therefore, these biomarkers indicate disease severity and progression of the disease [12]. High levels of these cytokines in urine highlight their proven use in non-invasive diagnostics, which offer high sensitivity and specificity for early detection [11]. Furthermore, their role in tumor progression via immune evasion mechanisms points to the urgent need for therapies targeting IL-mediated pathways. IL-15 combined with BCG shows an improved immune response and is a novel approach for bladder cancer immunotherapy [17]. Future studies should be directed toward optimizing cytokine-based therapies, especially in metastatic cases where IL-6 and IL-8 levels can predict therapeutic outcomes [18].

Among others, IL-6 and IL-8 are found to be important markers of chronic inflammation and urothelial damage in interstitial cystitis/bladder pain syndrome [19–21]. Both of these interleukins are associated with higher levels of symptoms. Thus, both are proven biomarkers. The inhibition of the IL-mediated pathways may be helpful in symptom management and in enhancing the quality of life of such patients [24]. Anti-inflammatory cytokines, like IL-10, could provide alternative approaches for symptomatic treatment based on blocking excessive responses [25].

In BPH, IL-6 and IL-8 are implicated in promoting inflammation, proliferation, and tissue remodeling [30]. Genetic variations within IL-10 suggest its critical regulatory role in constraining the inflammatory response, making it a promising target of intervention [33]. IL-17 and IL-18

Table 3. Roles of interleukins in urological diseases.

Disease	Interleukin	Role/Impact
Bladder cancer	IL-6	Biomarker for disease severity and progression; promotes immune evasion and angiogenesis [11,12].
	IL-8	Recruits tumor-associated macrophages (M2); linked to recurrence and immune checkpoint responses [13,14].
	IL-1β	Associated with vascular and lymphatic invasion; promotes tumor progression [15].
	IL-15	Enhances the efficacy of BCG therapy by activating NK cells and CD8+ T cells [17].
IC/BPS	IL-6	Activates the JAK/STAT3 pathway, leading to chronic inflammation and epithelial barrier disruption [19].
	IL-8	Activates mast cells, amplifying inflammation [19–21].
	IL-17	Drives chronic inflammation and fibrosis and contributes to epithelial barrier disruption [22,23].
	IL-10	Suppresses inflammation and promotes tissue repair, but systemic immunosuppression limits clinical use [24,25].
BPH	IL-6	Promotes inflammation, cellular proliferation, and tissue remodeling [29,30].
	IL-8	Enhances angiogenesis and smooth muscle contractility [30,31].
	IL-10	Anti-inflammatory; genetic polymorphisms are associated with prostate size and PSA levels [33,34].
	IL-17	Induces fibrosis and tissue remodeling, contributing to disease progression [36].
	IL-18	Correlates with prostate volume and inflammation severity; promotes fibrosis and hypercontractility [35,37].
RCC	IL-2	Induces cytotoxic T-cell activity; cornerstone of immunotherapy but associated with toxicity challenges [42].
	IL-4/IL-13	Promote tumor-induced immunosuppression; potential therapeutic targets in advanced RCC [47,48].
	IL-6	Supports tumor growth and immune suppression [51].
	IL-1β	Contributes to tumor progression and angiogenesis [51].
UTIs	IL-6	Biomarker for infection severity; correlates with pyelonephritis progression [52,53].
	IL-8	Recruits neutrophils to infection sites; aids in differentiation between upper and lower UTIs [54,56].
	IL-10	Regulates excessive immune responses, preventing tissue damage [53,58].
	IL-17	Promotes bacterial clearance in females but is dysregulated in males, leading to chronic infections [59].
	IL-22	Enhances epithelial repair and antimicrobial defenses [60].
Urolithiasis	IL-6	Mediates inflammation and calcium metabolism dysregulation; promotes stone formation [68,70,71].
	IL-8	Facilitates leukocyte recruitment and inflammation and correlates with stone size and severity [68,73].
	IL-1β	Associated with hypercalciuria and calcium oxalate stone formation; genetic polymorphisms increase risk [67,72].
	IL-18	Contributes to inflammation and oxidative stress, promoting calcium oxalate stone formation [66,72].
	IL-2	Typically reduces the risk of upper urinary tract stones but paradoxically elevated during progression [76].

BCG, Bacillus Calmette-Guérin; NK, natural killer; PSA, Prostate-Specific Antigen.

further contribute to fibrosis and smooth muscle hypercontractility, thus linking the activity of interleukin to disease progression [37,59]. Accordingly, inhibition of the IL-6 and IL-17 pathways is emerging as a novel strategy in the management of symptomatology and disease progression of BPH because of similar effects of ILs in both tumoral cells and normal cells in prostate tissue but further studies are needed to use these treatments in BPH [38,39].

IL-2-based immunotherapy is one of the cornerstones of treatment in renal cell carcinoma, inducing cytotoxic T-cell activity. Further refinements are required in relation to toxicity-related challenges that include IL-2 variants with increased selectivity [43]. In addition, IL-4 and IL-13 pathways have emerged as ways to surmount tumor-induced immunosuppression, while the modulation of IL-6 and IL-1β may suppress tumor-promoting inflammation [47,48,51]. Combination therapies involving IL-2 and immune checkpoint inhibitors merit further exploration in an effort to enhance efficacy while limiting side effects [46].

In UTIs, IL-6 and IL-8 act as biomarkers of infection severity and progression, thus aiding in early diagnosis and discrimination between upper and lower tract infections [52,56,61,62]. Anti-inflammatory IL-10 controls the immune responses to prevent tissue injury in severe infections [63]. IL-17 and IL-22 demonstrated sex-specific immune responses and highlighted the importance of personalized approaches in managing chronic UTIs [59]. Further modulation of IL pathways for enhancing antimicrobial responses with minimal tissue injury is a promising direction in therapeutic development [62].

The involvement of ILs in urolithiasis emphasizes the interconnection between inflammation and the process of stone formation. Here, critical players such as IL-6, IL-8, and IL-18 play a critical role in promoting inflammation, calcium release, and tissue remodeling [69–71]. Genetic studies of IL-1β and IL-18 polymorphisms, which are associated with the predisposition to form stones, identify opportunities for personalized therapies [67]. Anti-inflammatory treatments using IL pathways may contribute to lower recurrence rates and slow the progression of calculi; therefore, they need further clinical testing [71,79,80].

Further development of IL-targeting therapies has uncovered promising directions for successful treatment outcomes in the most widespread urological diseases. Modi-

fied IL-2 variants, such as PEG-IL-2, reduce toxicity while enhancing anti-tumor immune responses [43,44]. The combination of IL-15 with BCG has shown outstanding improvements in bladder cancer immunotherapeutic strategies that prove the value of synergistic approaches [17]. Furthermore, encapsulation strategies of IL-10 delivery bear the potential for minimizing systemic immunosuppression and enhancing the therapeutic precision of the latter [25]. These developments also open new horizons for more effective and better-targeted interventions in the management of complex urological conditions.

The dual roles of IL-6 and IL-8 in inflammation and immune modulation are evident in several urological diseases. For clarity, their contributions are summarized in Table 2 (Ref. [11–14,19–21,29–31,42,51–53,55,56,67,68,70,76]).

This review has demonstrated the multifaceted roles that interleukins play across urological diseases, including diagnostic biomarkers, prognostic predictors, and their use as therapeutic targets. However, some challenges are yet to be overcome, including (1) the determination of standardized protocols for measuring IL levels both in urine and serum for clinical use; (2) addressing genetic polymorphisms involved in cytokine expression, which raises the issue of individualized treatment approaches; and (3) the further development of IL inhibitors and therapies modulating cytokines, requiring further preclinical and clinical studies [12]. Further studies will be needed to confirm these observations in more extensive trials and combination therapies using interleukin pathways. Advances in cytokine engineering and immunomodulatory agents have opened new avenues toward improving patient outcomes in various urological diseases.

The roles and impacts of the interleukins discussed in this review are summarized in Table 3 (Ref. [11–15,17,19–25,29–31,33–37,42,47,48,51–54,56,58–60,66–68,70–73,76]).

Conclusion

Interleukins (ILs) play a central role in the immunopathology, diagnosis, and treatment of various urological diseases. Their involvement in inflammation, immune modulation, and tissue remodeling establishes them as critical biomarkers and therapeutic targets for bladder cancer, benign prostatic hyperplasia, renal cell carcinoma, urinary tract infections, interstitial cystitis, and urolithiasis. IL-6, IL-8, and IL-18 are considered key mediators in the progression and severity of diseases, whereas IL-10 has anti-inflammatory activity and thus holds therapeutic promise. Finally, the latest developments in cytokine-based therapies, including immunotherapies targeting ILs and biomarkers, will suggest promising directions for personalized medicine. Future research should focus on refining interleukin-targeted treatments and developing standardized diagnostic protocols to enhance clinical outcomes in urological diseases.

Availability of Data and Materials

Not applicable.

Author Contributions

HA, BB, HCK, and GC collected and analyzed the literature. HA and GC provided help and advice on the structure and content of the paper. HA, BB, HCK, and GC wrote the manuscript. HA and GC critically reviewed the final version of the manuscript. All authors contributed significantly to editorial changes of significant content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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