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Innate immunity and urinary tract infection

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Abstract

Urinary tract infections are a severe public health problem. The emergence and spread of antimicrobial resistance among uropathogens threatens to further compromise the quality of life and health of people who develop acute and recurrent upper and lower urinary tract infections. The host defense mechanisms that prevent invasive bacterial infection are not entirely delineated. However, recent evidence suggests that versatile innate immune defenses play a key role in shielding the urinary tract from invading uropathogens. Over the last decade, considerable advances have been made in defining the innate mechanisms that maintain immune homeostasis in the kidney and urinary tract. When these innate defenses are compromised or dysregulated, pathogen susceptibility increases. The objective of this review is to provide an overview of how basic science discoveries are elucidating essential innate host defenses in the kidney and urinary tract. In doing so, we highlight how these findings may ultimately translate into the clinic as new biomarkers or therapies for urinary tract infection.

Keywords

Urinary tract infection; Innate immunity; Pyelonephritis; Pattern Recognition Receptors; Cytokines; Antimicrobial Peptides

Introduction

Bacterial urinary tract infections (UTIs) constitute a common cause of significant morbidity in all pediatric patients. The most common bacterial cause of UTI in children is uropathogenic *Escherichia coli* (UPEC), which accounts for approximately 80% of cases [1].

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Acutely, ascending UTI can lead to pyelonephritis, acute kidney injury, renal abscess formation, and bacteremia. Chronically, UTIs can result in renal scarring, proteinuria, hypertension, and chronic kidney disease. Mounting evidence points toward complex roles of the innate immune system in UTI, functioning acutely to eliminate invading uropathogens and chronically to drive renal parenchymal injury and scarring. The purpose of this educational review is to highlight our current understanding of the contributions of innate immunity during UTI.

Overview of the innate immune system

In contrast to the adaptive immune response, the innate immune system generates a more rapid response to microbial challenge. When the innate immune system is compromised or dysregulated, signs of progressive inflammation and infection become clinically apparent [2]. In general, the innate immune system is composed of (1) pattern recognition receptors like toll-like receptors (TLR); (2) plasma proteins, chemokines, and cytokines; (3) cellular components like epithelial cells, bone marrow-derived phagocytes, dendritic cells, and natural killer cells; (4) toxic molecules such as reactive oxygen and reactive nitrogen intermediates; and (5) antimicrobial peptides (AMPs). Additionally, normally present local microbiota in the urogenital system and intestinal tract serve as another source of innate immunity, altering the pH of the local environment and producing their own antimicrobial products to help control UTI, as well as simply acting as competitive inhibitors of more virulent bacterial strains such as UPEC. When innate immune cells encounter potential pathogens, they activate intracellular signaling cascades that lead to the production of antimicrobial mediators, cytokines, and chemokines that orchestrate a local immune response. Epithelial cells make essential contributions to innate immunity by serving as physical barriers, communicating with hematopoietic cells, producing cytokines and chemokines, and secreting antimicrobial proteins and peptides that kill invading pathogens [3–7].

Molecular Targets of Innate Immunity

A. Pattern Recognition Receptors:

One of the most important elements in host-pathogen interactions is the ability of the host to identify external pathogens from self and elicit an appropriate response. Pattern recognition receptors (PRR) are one such host mechanism that detects pathogen- or damage-associated molecular patterns (PAMPs or DAMPs, respectively) and activates the innate immune response. PRR tend to be located on antigen-presenting immune cells like dendritic cells and macrophages. However, PRR can also be expressed by other immune and non-immune cells. These receptors generally localize to cell surfaces but they can also be intracellular, located in either the cytoplasm or in endosomes. The type of PRR activated is both pathogen- and location-specific [8]. Broadly, PRR activation initiates cellular signaling cascades that trigger transcription of genes involved in host defense. Specifically, PRR activate Nuclear Factor kappa B (NF-κB) signaling, downstream cytokine and chemokine expression, and inflammatory cell recruitment for phagocytosis and bacterial clearance [9].

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TLRs are one of the most important and thoroughly investigated families of PRRs. TLRs are characterized by the presence of a large extracellular domain of leucine-rich repeats, a transmembrane segment, and a cytoplasmic Toll/Interleukin—1 receptor-like (TIR) domain which helps mediate the interaction between ligand binding and intracellular signaling proteins. TLRs play an essential role in the innate recognition of microbial components and have been heavily equated with initiating innate defense in the setting of UTIs [10, 11]. When uropathogens enter the urinary tract, they trigger a conformational change in the receptor to activate defined adaptor molecules that mediate different cascading responses, including the release of chemokines, interferons, interleukins (IL), antimicrobial substances, and proinflammatory cytokines (Figure 1). The molecular activation of different TLR-family members has been reviewed in detail elsewhere [10, 11].

TLR2, TLR4, TLR5, and TLR11 have been shown to regulate UTI susceptibility [10, 11]. Of these, the best studied is TLR4, whose ligand is the Gram-negative bacterial cell wall component, lipopolysaccharide (Lps). TLR4 controls the earliest steps of the mucosal response towards UPEC. Certain inbred mouse strains harbor a point mutation in the TIR-domain of TLR4 that renders them resistant to endotoxin, but highly susceptible to Gram-negative infections including UTI [12]. Subsequent studies have shown that TLR4 expression on bladder epithelial cells as well as innate immune cells is required to successfully combat invasive UPEC infection [13–15]. In the kidney, TLR4 and TLR5 signaling in renal collecting duct cells play key roles in UPEC clearance during pyelonephritis [16, 17]. The following are excellent reviews on TLR-signaling and innate defense of the urinary tract [10, 11, 18].

While TLR signaling activates the host innate immune response, it can also play a pathologic role by activating inflammatory responses that damage local tissues. Specifically, TLR signaling may play a role in initiating and perpetuating renal damage in the setting of UTI. Fortunately, there are innate regulatory mechanisms to fine-tune TLR signaling in order to ensure appropriate response selectively. These include reliance on co-receptors, receptor folding, post-translational modifications, cleavage, intracellular trafficking, and the presence of negative regulators [19].

Additional evidence in human and UPEC genomes attests to the central role of Lps-TLR4 as a critical ligand-receptor interaction during UTI pathogenesis. In humans, polymorphisms in the *TLR4* gene have been associated with the development of recurrent UTI [20, 21]. In UPEC, mutations in operons for Lps biosynthesis suppress the ability of bladder epithelial cells to secrete cytokines and chemokines. Moreover, certain UPEC genomes contain TLR4-TIR domain containing proteins (Tcps) that suppress TLR signaling. In one study, approximately 40% of UPEC isolated from patients with acute pyelonephritis had these Tcps, as compared to between 16-21% in patients with asymptomatic bacteriuria and cystitis. In experimental UTI, bacteria encoding Tcp had better survival and resulted in worse renal pathology [22]. As such, Tcps act as bacterial virulence factors to suppress innate immunity and increase UTI susceptibility. Together, these observations link defects in TLR4 expression and signaling to heightened UTI risk.

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B. Interferon Regulatory Factors

Interferon Regulatory Factor (IRF)-3 and IRF-7 are transcription factors induced during UTI as a result of TLR activation [23, 24] (Figure 1). While both act as transcriptional activators, IRF-3 and IRF-7 exert opposing effects during UTI. IRF-3 is dependent on TLR4 activation and important in regulating the antibacterial response [23]. Mice that lack *Irf3* develop severe acute pyelonephritis in experimental UTI. This is accompanied by massive tissue damage, significant mucosal and urine neutrophil accumulation, and increased tissue and urine bacterial burden [23]. In contrast, IRF-7 appears to drive the inflammatory response. Accordingly, *Irf7* KO mice experience lower neutrophil recruitment and UPEC burden than *Irf3* KO and wild type mice in response to experimental UTI. Evaluation of gene profiles between *Irf3* and *Irf7* KO mice confirms that the hyperinflammatory response during UTI is driven by IRF-7 [23, 24]. Thus, it appears that IRF-3 and IRF-7 expression balance each other to mount an effective, limited innate immune response to bacterial infection.

Genetic variants of *IRF3* and *IRF7* expression may affect human UTI susceptibility. Clinical evaluation has found that children with recurrent acute pyelonephritis have a hypomorphic *IRF*3 promoter compared to children with asymptomatic bacteriuria [23]. In contrast, *IRF7* promoter polymorphisms conferring lower *IRF7* expression were protective against recurrent acute pyelonephritis in children and more commonly associated with asymptomatic bacteriuria [24]. In addition, suppressing *Irf7* expression in pyelonephritis-susceptible *Irf3* KO mice was actually protective of UTI and renal tissue damage [24]. In fact, *Irf7* suppression was comparable to antibiotic therapy in regards to preventing renal abscess formation, suggesting IRF-7 could serve as a target of immunotherapy in limiting UTI pathogenesis [24].

C. Chemokines and Cytokines

Cytokine signaling plays a seminal role in coordinating the innate immune response during UTI [25–27]. Cytokines broadly refer to small proteins made intracellularly that are released to enable cell-to-cell communication through autocrine, paracrine, and/or endocrine actions. Interleukins (ILs) are cytokines typically made by inflammatory cells with action on inflammatory cells, while chemokines are cytokines with chemotactic properties. Interestingly, mucosa-derived cytokine expression was first observed in the setting of UTI [28]. As highlighted below, extensive investigation has been performed on the roles of IL-6 and IL-8 during UTI.

Studies suggest that IL-6 plays a role in UTI prevention through multiple mechanisms [29, 30]. IL-6 expression localizes to the bladder urothelium and induces AMP expression to facilitate UPEC clearance [27, 29] (Figure 2). Additionally, IL-6 regulates monocyte proliferation and alters iron homeostasis to impede intramacrophage UPEC growth [31, 32]. When IL-6 knockout mice are subjected to experimental UTI, they experience higher mortality rates, more severe renal histopathology, and higher renal UPEC burden than wild type controls [29, 30]. During early cystitis, IL-6 deficiency leads to increased numbers of UPEC intracellular bacterial communities (IBC), which allow UPEC to evade the innate immune system and contribute to UTI chronicity [29]. This body of work suggests that IL-6 signaling may be developed as a target to treat acute UTI or prevent recurrent infections.

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Recent findings also suggest that IL-6 may be a novel UTI biomarker. Murine UTI models demonstrate that serum and urinary concentrations of IL-6 increase during UTI in a TLR4-dependent manner [29, 33]. Clinically, serum and urine concentrations of IL-6 correlate to the degree of UTI severity. Specifically, children with pyelonephritis have higher IL-6 serum and urine concentrations than children with cystitis. In the pyelonephritis cohort, children with acquired renal scars had higher IL-6 concentrations than those without scars [34–36]. Thus, future prospective studies can evaluate the role of IL-6 as an acute UTI biomarker (cystitis vs. pyelonephritis) or a prospective marker for chronic renal injury and scarring.

Like IL-6, IL-8 transcription is linked to TLR4 activation. IL-8 (also known as CXCL8) belongs to the CXC family of chemokines. IL-8 plays an important role in inflammatory cell chemotaxis, particularly neutrophil recruitment during UTI [13, 34, 37]. IL-8 is expressed both by infected epithelial and circulating cells, as well as recruited immune cells. Neutrophils migrate towards gradients of IL-8 to phagocytose and kill bacteria. In the urinary tract, IL-8 facilitates transepithelial neutrophil migration in the urothelium, permitting neutrophil trafficking from the blood through tissue and across the mucosa to enter the urine [37]. As a result, IL-8 level correlate with the presence of urinary leukocytes and is responsible for the pyuria seen in UTI [18] (Figure 2).

IL-8 has two cell surface receptors: CXCR1 (IL-8RA) and CXCR2 (IL-8RB). CXCR1 is more specific for binding IL-8, whereas CXCR2 is more promiscuous and can bind to multiple CXC chemokines. Both CXCR1 and CXCR2 are expressed on urothelial cells (Figure 2). Their expression increases in the setting of infection to enhance IL-8-dependent neutrophil migration [18, 37]. CXCR1 in particular is thought to be essential for increased neutrophil migration across infected cells *in vitro*, as antibodies specific to CXCR1 inhibit this process compared to antibodies against CXCR2. This has been confirmed *in vivo* where neutrophils in mice lacking the murine homologue of the CXCR1 receptor are unable to migrate across the urothelial border into the bladder lumen and thus accumulate in the subepithelial layer [37]. Consequently, these mice are unable to clear UPEC from their bladder and kidneys with resulting renal abscess formation, scarring, and bacteremia [38, 39]. Children prone to acute pyelonephritis have also been found to have reduced CXCR1 levels as compared to age-matched controls [38]. In part, this may be due to *CXCR1* and *CXCR2* polymorphisms, suggesting that variations in these genes may provide predictive markers to determine UTI susceptibility [40].

D. Antimicrobial Peptides

Host defense peptides and proteins, also known as AMPs, are short, cationic oligopeptides that are evolutionarily conserved. AMPs represent a diverse class of molecules, including defensins, cathelicidin, ribonucleases, and metal-binding proteins. The field of study of AMPs has been steadily expanding over the past decade, suggesting that these molecules have captured the interest of a number of research programs investigating different disease states [41]. In humans, these peptides are expressed by epithelial tissues that often come into contact with pathogenic microorganisms, such as the bladder urothelium and renal collecting duct (Table 1). Additionally, AMPs are expressed in immune cells that are recruited to sites of injury and infection. Table 1 summarizes the epithelial-derived AMPs expressed in the

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human urinary tract and highlights studies showing their antibacterial activity and biological relevance.

The most direct application of AMPs to clinical medicine is their development as novel antimicrobials for UTI as well as other common infections. Limitations in their direct delivery have been addressed by methods to induce endogenous AMP production, such as using short chain fatty acid derivatives like butyrate, vitamin D3 derivatives, and estrogens [42–44]. Recent data also suggest that AMPs can be developed as UTI prognostics or diagnostics. Auxiliary studies to the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial show that genetic copy number variation of in the alpha defensin *DEFA1A3* locus in children with vesicoureteral reflux predict recurrent UTI [45]. AMPs have also been employed as an adjunct tool in addition to leukocyte esterase for diagnosing UTI in children [46]. Urinary levels of NGAL correlate negatively with recurrent UTI risk, and NGAL has been suggested as an additional biomarker for UTI in children [47, 48]. The role of AMPs in UTI has been reviewed extensively elsewhere [2, 5, 49].

Cellular Mechanisms of Innate Immunity—The innate immune response to UTI is orchestrated through close collaboration between epithelial cells and leukocytes, summarized in Table 2 and illustrated in Figure 3. The urothelial cells lining the bladder, ureter, and renal pelvis, as well as the intercalated cells (IC) of the renal collecting duct have been implicated in early innate defense against uropathogens. This occurs through a number of mechanisms including: (1) detection of bacteria by PRR expression; (2) AMP production; (3) expulsion of intracellular bacteria; (5) production of cytokines such as IL-6; (6) production of IL-8 and other chemokines that promote phagocyte recruitment; (7) barrier function; and (8) regulated exfoliation and regeneration [38, 50–52].

Recent genetic studies have established an essential role for IC during UTI. In one approach, IC depletion was achieved through deletion of the *Car2* gene encoding carbonic anhydrase 2, which serves a critical function in maintaining electrochemical gradients in the IC [53]. *Car2* knockout mice exhibit a 4-fold decrease in IC number and are more susceptible to pyelonephritis following transurethral UPEC inoculation [53]. Alternatively, the consequences of IC depletion on UTI susceptibility were investigated by deletion of an essential transcription factor for IC development, *Tcfcp2l1* [54]. Like *Car2* knockouts, *Tcfcp2l1* deficiency leads to increased bacterial burden following transurethral UPEC inoculation. Using a condition knockout strategy, we have recently demonstrated that the insulin receptor (IR) is essential for AMP production and UPEC clearance by IC [55]. IR deletion does not impact IC number; rather, insulin is responsible for AMP production by IC in a manner dependent on the phosphatidylinositol-3-kinase signaling pathway [55, 56].

Essential interactions between tubular epithelial cells and mononuclear phagocytes have been implicated in forming an intercellular network in the kidney (Figure 3A) [57]. Renal medullary epithelial cells express a transcription factor, NFAT5, that regulates the secretion of chemokines in response to increasing extracellular sodium. The medullary sodium gradient, which classically functions to promote urine concentration, is also required for monocyte-derived mononuclear phagocytes (MNP) to localize to the renal medulla. The hypersaline microenvironment of the medulla also drives bactericidal and neutrophil

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chemotactic activities of MNPs. Disruption of the medullary sodium gradient in mice and patients with nephrogenic diabetes insipidus results in increased UTI susceptibility [57]. This elegant work, supported by human data, illustrates the manner in which the unique physiology of the kidney can modulate the innate immune response.

Svanborg and colleagues established the importance of neutrophils for UTI eradication [58]. Recruitment of neutrophils was shown to be reliant on bacterial Lps, as Lps-resistant mice lacked neutrophil recruitment and this was associated with bacterial persistence in the bladder and kidneys. When neutrophils were depleted from Lps-sensitive mice prior to infection, UPEC clearance from the urinary tract was impaired [58]. In addition to their essential role in bacterial killing, activated neutrophils are capable of causing extensive parenchymal injury in the infected urinary tract. Neutrophil-derived cyclooxygenase-2 (COX-2) has been implicated as a driver of inflammation associated with severe, recurrent cystitis [59]. Neutrophils are responsible for severe tubulointerstitial nephritis in IL-8 receptor-deficient mice [38, 39]. Thus, the fine-tuning of the neutrophil response is essential to balance their bactericidal function against their propensity to cause tissue injury.

Monocytes and macrophages are well-suited to modulate neutrophil function during UTI. Elegant experiments from the Engel laboratory established that complex interactions between neutrophils, resident macrophages, and recruited inflammatory monocytes trigger neutrophil migration across the urothelium during cystitis (Figure 3B) [60], In response to UTI, inflammatory monocytes are recruited to the bladder submucosa and produce the cytokine, Tumor Necrosis Factor (TNF)-α. Next, TNF-α engages its receptor on resident macrophages, leading to secretion of the Cxcl2 chemokine. Finally, Cxcl2 engages the Ccr2 receptor on neutrophils, leading to production of the Mmp9 matrix metalloproteinase. Mmp9 degrades the extracellular matrix lining the urothelial basement membrane, triggering transmigration of neutrophils [60]. Further studies are required to determine if this licensing of neutrophil migration by monocyte-macrophage interactions is applicable during pyelonephritis.

The natural killer (NK) and NK-T lineages have been implicated in host defense during UTI. Invariant NK-T cells are activated by the ligand, α-galactosylceramide (α-GalCer). Administration of α-GalCer leads to reduced kidney bacterial burden during Gram-negative and Gram-positive UTI, associated with higher levels of IL-12, IFN-γ, and TNF-α compared to control glycolipids [61]. More recent experiments have implicated NK cells as critical responders to UPEC, by recognition of bacterial type I pili and production of TNF-α [62]. Optimal NK cell and neutrophil recruitment during UTI requires urothelial cell secretion of the chemokine, Stromal Cell-Derived Factor 1, another example of the collaborative network linking epithelial cells and leukocytes in urinary tract defense [63].

A landmark historical study established that mast cells (MC) are critical mediators of neutrophil activation during Gram-negative bacterial infections through production of TNF-α in a manner dependent on the bacterial fimbrial protein, FimH [64]. Likewise, MC produce TNF-α following UPEC exposure in *a* FimH-dependent manner, and MC-deficient mice display impaired UPEC clearance during experimental UTI associated with reduced neutrophil recruitment [65]. A recent study has revealed a critical role for MC in triggering

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exfoliation of bladder umbrella cells during acute cystitis [51]. Following transurethral inoculation of UPEC, umbrella cells secrete the cytokine, IL-1β, which induces MC to migrate to a position immediately deep to the umbrella cell. These MC degranulate locally, and umbrella cells endocytose MC granules containing chymase. Once chymase reaches the umbrella cell cytosol, it triggers cleavage and activation of caspase-1, which mediates cytolysis and exfoliation [51]. Thus, MC serve multiple essential roles in coordinating the innate immune response.

Conclusions

The innate immune system plays an essential role in the prevention of recurrent and invasive UTI, but failure to dampen the innate immune response may lead to irreparable parenchymal injury. This raises the prediction that, in select cases, modulation of the innate immune system may facilitate clinical management of UTI in the future. A potential future strategy in the prevention of intractable UTIs or multi-drug resistant UTIs will be to combine antimicrobial therapy with innate immune modulators. Unlike conventional antibiotics, such immunomodulatory therapies will not be universally applicable. Instead, they will need to be tailored to each patient and take into account the patient's age, genetic profile, immune competence, pathogen virulence and antibiotic susceptibility. For these novel strategies to be safe and effective, a thorough comprehension of the host innate immune response will be required.

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Key summary points

- A well-coordinated and effective innate immune response balances the need to promptly clear invading pathogens while minimizing inflammatory responses that disrupt epithelial barriers and cause cellular injury.
- Cross-talk between different innate immune mechanisms coordinates the recruitment or activation of leukocytes, transcription factor activation, and the release of epithelial peptides and proteins to facilitate pathogen clearance.
- Genetic mutations in innate immune effectors, like TLRs, transcription factors, and AMPs, may increase UTI risk.
- Novel preclinical strategies have been described that can enhance innate immune defenses of the kidney and urinary tract to prevent and eradicate UTI.

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Multiple choice questions (answers after reference list)

1. Which of the following secreted proteins directly promotes neutrophil chemotaxis across the urothelium during UTI?

- **a.** IL-12
- **b.** TNF-α
- **c.** IL-8
- **d.** IL-6
- **e.** IL-1β

2. Which of the following cell types is *NOT* a source of TNF-α during UTI?

- **a.** Neutrophils
- **b.** Resident macrophages
- **c.** Mast cells
- **d.** Natural killer cells

3. What are the roles of mast cells during UTI?

- **a.** Promote exfoliation of bladder umbrella cells
- **b.** Secrete TNF-α, which promotes recruitment of circulating neutrophils
- **c.** Neither a nor b is correct.
- **d.** Both a and b are correct.

4. How do intercalated cells contribute to host defense against ascending UTI?

- **a.** Secrete TLR4 and TLR5, which bind to bacterial ligands and prevent kidney invasion
- **b.** Release antimicrobial peptides in an insulin dependent manner
- **c.** Exfoliate into the collecting duct lumen following UPEC binding
- **d.** Release chemokines that promote recruitment of circulating T and B lymphocytes

5. Which of the following is a form of innate immunity?

- **a.** Biological shielding through use of local microbiota
- **b.** Induction of AMP expression in the urinary stream
- **c.** Production of chemokines and chemokines
- **d.** Toll-like receptors
- **e.** All of the above

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Answers

1. c
2. a
3. d
4. b
5. e

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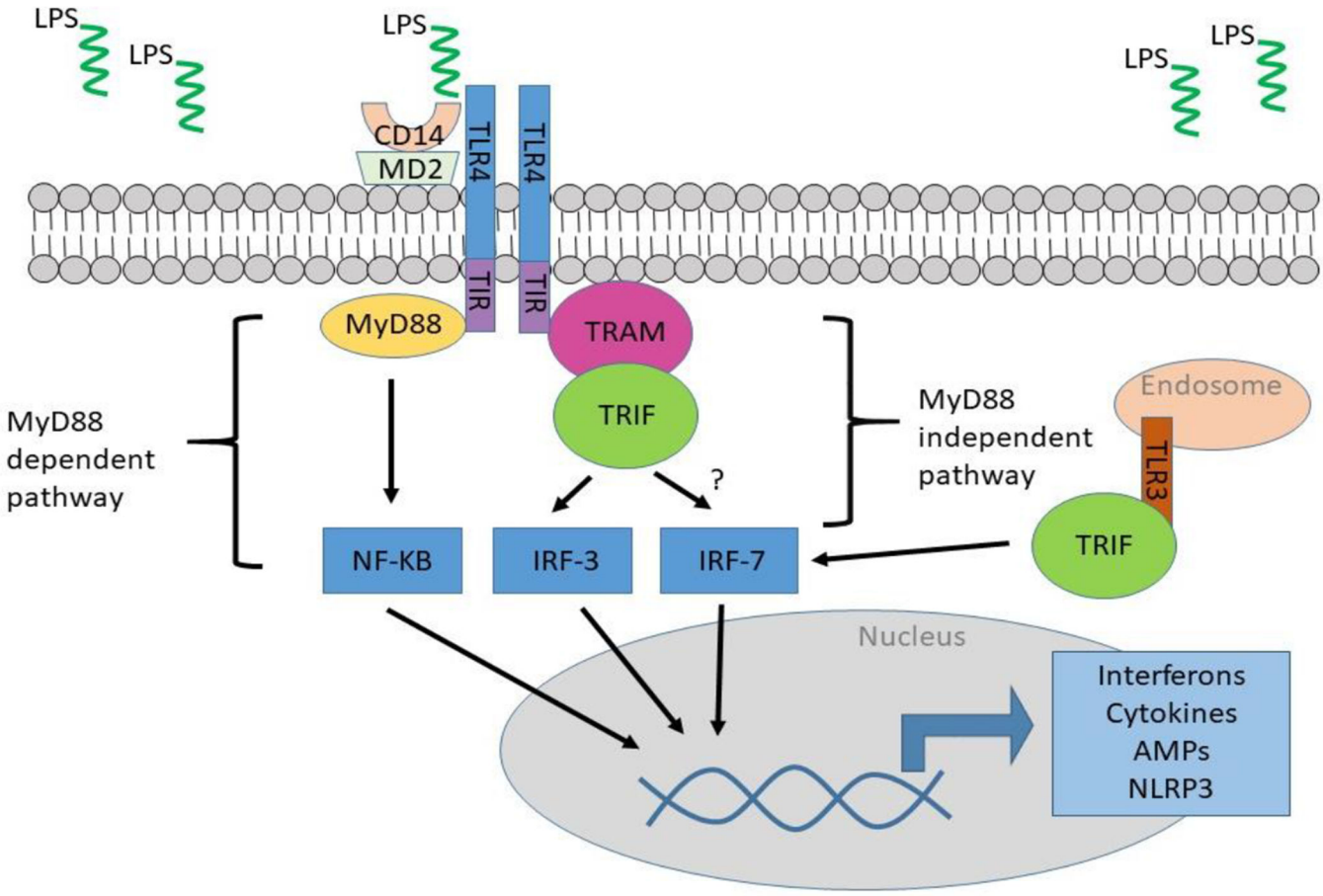

Figure 1.

TLR4 signaling cascade. TLR4 activation by Lps requires co-receptors CD14 and MD2. Signaling cascades are MyD88-dependent (via NF-κB) and MyD88-independent (via IRF-3 and IRF-7) and result in interferon, cytokine, antimicrobial peptide (AMP), and inflammasome expression.

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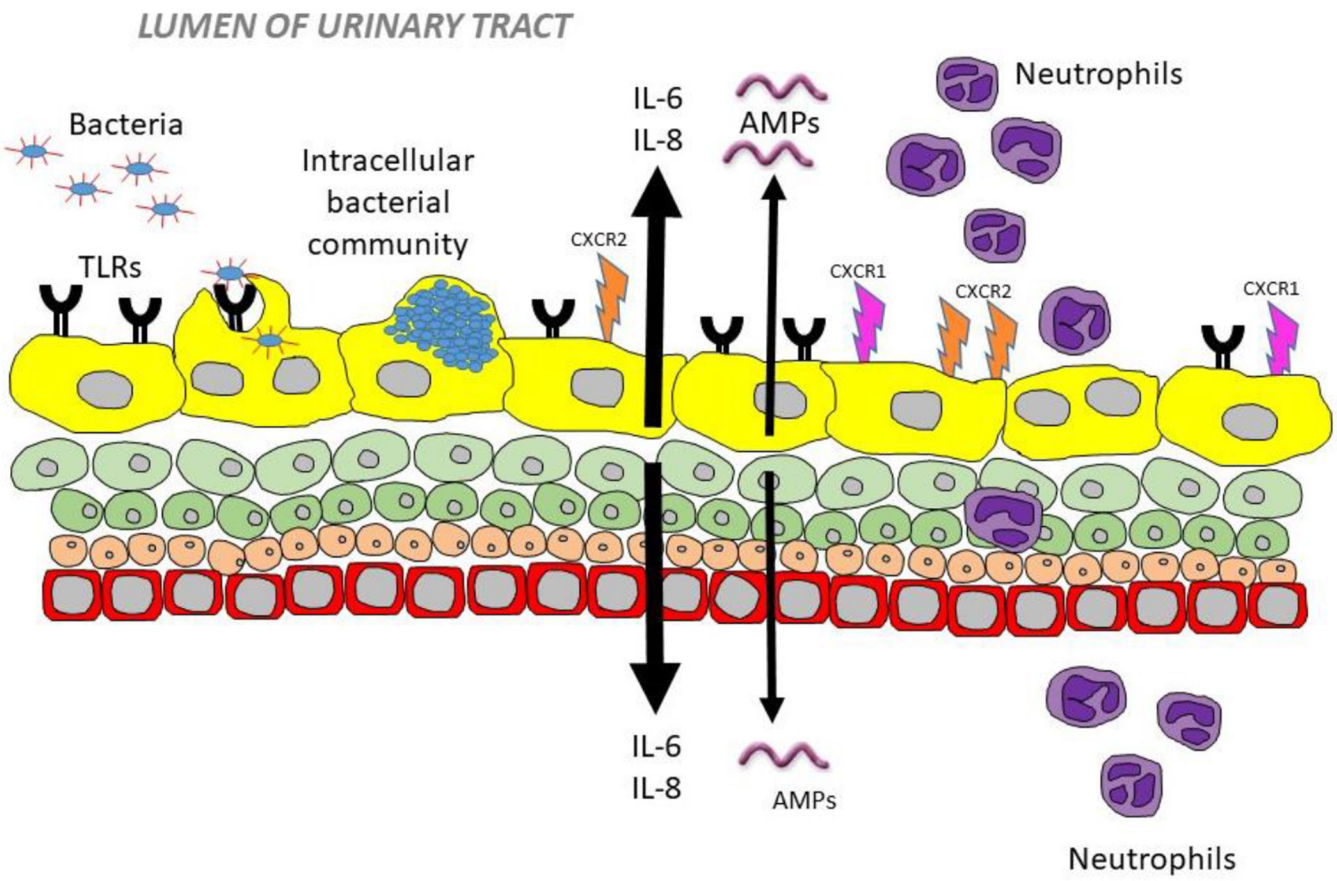

Figure 2.

Urothelial innate immunity. Bacteria bind to TLRs and form intracellular bacterial communities. UTI induces urothelial expression of the cytokine IL-6, which is involved in AMP expression, and the chemokine IL-8, which initiates neutrophil trafficking into the urinary space. Cell surface receptors CXCR1 and CXCR2 are expressed on urothelial cells to enhance neutrophil migration

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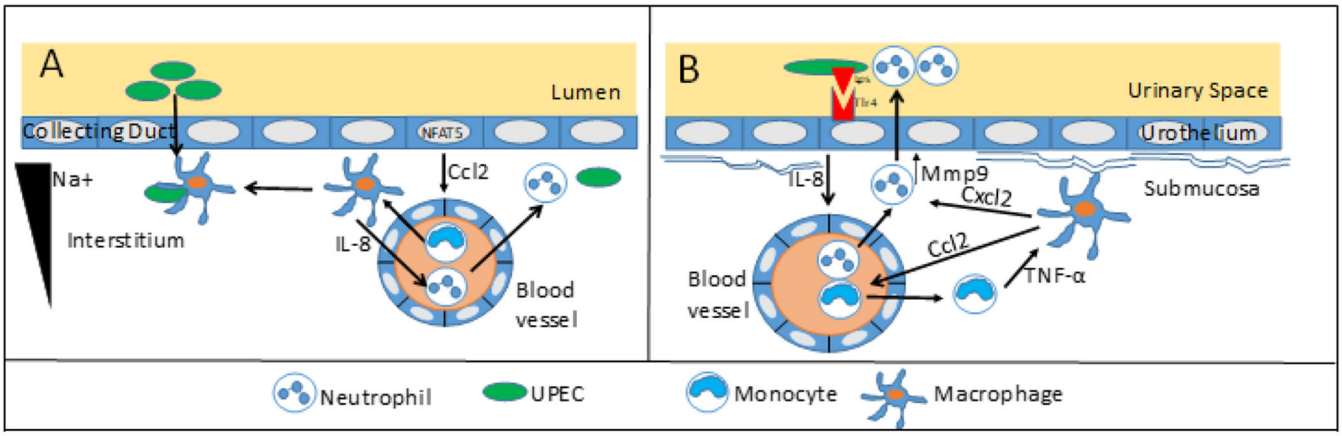

Figure 3.

Leukocyte-epithelial cell interactions orchestrate the innate immune response to UPEC (**A**) Tubular cells establish the medullary Na+ gradient and secrete the chemokine Ccl2 in a NFAT5 dependent manner. [57] Ccl2 recruits circulating monocytes, which differentiate into macrophages These macrophages increase phagocytosis, IL-8 dependent neutrophil recruitment, and antimicrobial activity in the presence of sodium. This network of myeloid cells serves a critical role in limiting interstitial spread of bacteria. (**B**) Urothelial cells express TLR4 that recognizes bacterial LPS, resulting in production of IL-8 that elicits neutrophil chemotaxis. Efficient neutrophil transepithelial migration relies on resident macrophages, which recruit circulating monocytes in a Ccl2-dependent manner. Monocyte TNF-α stimulates macrophages to secrete Cxcl2. Cxcl2 stimulates neutrophil production of Mmp9, which degrades matrix and promotes efficient transepithelial neutrophil migration to the urinary space.[37, 60]

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Table 1.

Epithelial Antimicrobial Peptides and Proteins Produced in the Urinary Tract

Name	Classification	Cellular Source	Biological Relevance
α-and β-defensins	AMP	Bladder Urothelium and Kidney Intercalated and Principal Cells	*Defb1*$^{-/-}$ mice exhibit increased rates of spontaneous bacteriuria [66].
Cathelicidin	AMP	Bladder Urothelium and Kidney Intercalated Cells	Increased kidney UPEC burden in *Camp*$^{-/-}$ mice after experimental UTI [67].
Ribonucleases	AMP	Bladder Urothelium and Kidney Intercalated Cells	RNase 4 and 7 neutralization promotes UPEC growth in human urine [68, 55].
Lipocalin 2	Siderophore	Bladder Urothelium and Kidney Intercalated Cells	Increased bladder UPEC burden in *Lcn2*$^{-/-}$ mice after experimental UTI [54, 69].
Hepcidin	Iron Regulation	Nephron and Collecting Duct	Increased bladder/kidney UPEC burden in mice after experimental UTI [70, 71].
Uromodulin	Glycoprotein	Loop of Henle	Increased bladder UPEC burden in *Thp*$^{-/-}$ mice after experimental UTI [72].

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Table 2:

Cellular Effectors of Innate Immunity During UTI

Cell	Mechanism
Urothelial cells	• Detect UPEC by expressing PRRs [50] • UPEC expulsion [52] • Secrete AMP [5] • Release chemokines that promote neutrophil chemotaxis [38] • Exfoliation and regeneration [51, 73]
Intercalated cells	• Detect ascending bacteria in a TLR4 and TLR5 dependent manner [16, 17] • Secrete AMP, some of which are regulated by insulin/PI-3 kinase signaling [5, 54, 55]
Monocyte derived phagocytes	• Regulate neutrophil recruitment during pyelonephritis [57] • Phagocytose and kill bacteria [57] • Regulated by medullary sodium gradient in an NFAT5-dependent manner [57]
Neutrophils	• Phagocytosis and bactericidal activity [58] • Prolonged recruitment and/or activation may promote tissue injury and infection chronicity [38, 39, 59]
Inflammatory monocytes	• Recruited to the infected bladder and kidney from the peripheral blood and bone marrow • Secrete TNF-α , which indirectly promotes neutrophil recruitment during acute cystitis [60]
Resident macrophages	• Secrete Cxcl2 in a TNF-α dependent manner, which promotes secretion of matrix metalloproteinase essential for neutrophil transmigration across the urothelium [60]
Natural Killer cells	• Promote bacterial clearance by secreting TNF-α [62]
Natural Killer-T cells	• Promote bacterial clearance by cytokine secretion in response to activating glycolipids [61]
Mast cells	• Recruit neutrophils by producing TNF-α [64, 65] • Release cytolytic enzymes that trigger exfoliation of bladder umbrella cells [51]