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Urinary Tract Immunology

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1. Introduction

Urinary tract infection (UTI) is one of the most common infections in humans. It is estimated that 40% of women and 12% of men will experience a symptomatic UTI, with incidences peaking in their early 20s or after age 85, respectively (1). Approximately 25% of these women will experience recurrence within 6 to 12 months (1). Uropathogenic *Escherichia coli* (UPEC) is the most common etiological agent responsible for uncomplicated UTI. In the United States alone, the estimated annual societal cost of UTI is more than 3 billion dollars (1).

Despite significant advances in the understanding of UPEC biology, mechanistic details regarding the host response to UTI and full comprehension of genetic loci that influence susceptibility require additional work. As new and intriguing details of how uropathogens initiate infections and persist within the urinary tract have emerged, so has important information regarding how the immune system functions within the urinary tract. The complex cross-linking for innate and adaptive immune response as well as humoral and cellular effectors is the key to the urinary tract immune system and to its defense against pathogenic microorganisms. As antibiotic therapy becomes increasingly ineffective, modulating the innate and adaptive immune system in the urinary tract using TLR4 ligands and other immunomodulators may become viable options to combat UTIs.

2. Innate responses to urinary tract infections

2.1 Host factors that prevent colonization of urinary tract with UPEC

Uroepithelial adherence is critical for establishment of UTI. The urinary tract, comprised of the urethra, bladder, ureters and the kidneys, represents a formidable mechanical barrier to infection. In addition to the relative impregnability of the epithelium lining the tract, potential pathogens have to contend with the powerful flushing action of urine and the aggregating actions of urinary mucins (2;3). UPEC strains possess an impressive repertoire of adhesins that enable them to aggregate and adhere to cellular surfaces (4). Consequently, the first line of host defense against UTI is concentrated on preventing UPEC adherence to the bladder mucosa. The luminal surface of the bladder is lined with highly sulfated and anionic glycosaminoglycans (GAGs) that contribute to bladder wall impermeability and afford an antimicrobial anti-adherence property. Intuitively, urine flow seems to be a convenient defense mechanism; however, FimH binds to mannose moieties using "catch-

bonds," interactions that are actually strengthened by the sheer stress induced during urine flow (5). Thus, more active mechanisms, like umbrella cell exfoliation (6) that occurs by an apoptosis-like mechanism and is promoted by FimH (7) remove adherent UPEC. Tamm-Horsfall protein (THP) is a high-molecular-weight protein present in human urine (8) that binds E. coli fimbriae (9) by virtue of its mannose moieties, inhibiting fimbrial interaction with uroplakin receptors (10). This phenotype translated in vivo as thp−/− mice were unable to control lower-UTI (11). THP also appears to act as an innate-adaptive immunoregulatory molecule that can activate dendritic cells (12).

2.2 Host signaling in response to UPEC recognition

Of the various immune surveillance molecules the Toll-like receptor (TLR) family is the best characterized (13-16). Unlike the receptor for the FimH adhesin of UPEC, which promotes bacterial invasion and subsequent invasion of BECs (17), the TLRs function by detecting different PAMPs and then mobilizing appropriate immune defences. The common TLRs encountered in the urinary tract include TLR2 (recognizes bacterial lipoteichoic acid or lipoprotein), TLR3 (recognizes double stranded RNA), TLR4 [recognizes lipopolysaccharides (LPS)], TLR5 (recognizes flagellin), TLR9 (recognizes unmethylated CpG DNA of bacteria and viruses), and TLR11 (recognizes profiling of parasites). TLR5 and TLR11 are other TLRs shown in *in vivo* studies to contribute to immune defence in the urinary tract (13;16). TLR5 is predominantly expressed on bladder cells whereas TLR11 is primarily on kidney cells (13;16). Perhaps the best studied of these TLRs is TLR4, which is well expressed on epithelial cells of the kidney and bladder (14).

Toll-like receptor 4 (TLR4) is important for signalling of innate immunity in response to UTI

Upon successful adherence to the uroepithelium, Toll-like receptor (TLR) recognition of pathogen-associated molecular patterns generates signaling cascades to control infection and direct adaptive responses (18). Particular close attention has been given to the role of TLR4 in UTIs. LR4 mutation (TLR4-/-) mice failed to initiate an immune response against UTI, and they developed an asymptomatic carrier state resembling human asymptomatic bacteriuria (ABU) (19) . Interestingly, recent studies have shown that TLR4 has antimicrobial roles that appear to be specific to the urinary tract (20) (21). These include promotion of IL-6 and IL-8 secretion by activation of the MyD88- or cAMP-dependent signaling pathway, inhibition of bladder epithelial cell (BEC) invasion by bacteria, and expulsion of UPEC harboring in BECs (21-24). Clinical research found that children with UTI have lower TLR4 expression than age-matched controls without UTI. In relation to UTI history, children with low TLR4 expression on their neutrophils display an asymptomatic bacteriuria (ABU) carrier state lacking both inflammation and bacterial clearance (25). Meanwhile, adult patients with chronic UTI were found to have lower TLR4 expression than healthy controls without UTI (26). All these imply that enhanced TLR4 expression possibly contributes to increased mucosal immune response.

It has been known that C3H/HeJ mice, harboring a mutation in the Toll/interleukin-1 receptor (TIR) domain of TLR4, cannot resolve UTI as efficiently as LPS-responsive C3H/HeN counterparts (27). In accordance, tlr4−/− mice had significantly higher bacterial burdens in their bladders than similarly infected wild-type mice (28). This clearance defect is the result of insufficient downstream cytokine and chemokine production and neutrophil recruitment (29). Data from mouse chimeras disclosed that TLR4 on both stromal and

hematopoietic cells is critical for normal inflammatory responses and clearance of UPEC in the bladder and kidney (30). Correspondingly, children with low TLR4 expression on their neutrophils display an asymptomatic bacteriuria (ABU) carrier state lacking both inflammation and bacterial clearance (25). A similar response is exhibited by C3N/HeJ mice following UPEC inoculation (31).

TLR4-mediated signaling is mainly LPS independent

TLR4-mediated signaling in the urinary tract does not appear to be the result of the archetypal interaction with LPS. Both the role of LPS in and the molecular trigger of TLR4 signaling by UPEC are topics of debate (32). Studies using the A498 human kidney cell line indicate that TLR4 signaling in response to UPEC requires P fimbriae and can be mediated independently of LPS (33). Mechanistic details regarding this phenomenon include P fimbriae binding to surface glycosphingolipids (GSLs) and subsequent release of the GSL membrane-anchoring domain, ceramide (34). Ceramide appears to act as a TLR4 agonist and the putative intermediate for TLR4 signaling initiated by P fimbriae (34). Lastly, the FimH tip adhesin of type 1 fimbriae was recently shown to directly interact with TLR4, an additional means for LPS-independent stimulation by UPEC fimbriae (35)

TLR4-mediated signaling is also LPS dependent

In contrast to LPS-independent signaling by P fimbriae, there appears to be a cooperative stimulation of TLR4 by LPS and type 1 fimbriae (36). This cooperative stimulation directly correlates with the level of cluster of differentiation 14 (CD14) expression on bladder cells (24). CD14 is an accessory molecule required for optimal TLR4 signaling in response to LPS (24). Immunohistochemical (IHC) analysis of human bladder biopsies revealed that CD14 expression is localized to the submucosa (37), suggesting that uroepithelial cells exposed to the lumen have little to no CD14 expression and therefore may not respond efficiently to LPS alone. These results support a role for both independent and cooperative TLR4 stimulation by UPEC fimbriae.

Downstream signalling pathways important for signalling of innate immunity in response to UTI

Infection of knockout mice has revealed critical roles for myeloid differentiation primary response protein 88 (MyD88), TIR domain-containing adaptor inducing beta interferon (TRIF), and TRIF-related adaptor molecule (TRAM) in signaling for UPEC clearance (38). It is also apparent that different fimbrial types influence the corresponding downstream signaling pathways (38). Regardless of the fimbria involved in stimulation, all pathways involving these adaptor molecules result in activation of NF-κB and proinflammatory gene expression. Song and colleagues identified an accompanying proinflammatory bladder cell signaling pathway that is also dependent on TLR4 but results in a spike in intracellular calcium levels (39). This calcium spike leads to adenylyl cyclase 3 (AC3)-mediated increase in cAMP, protein kinase A (PKA) activation, phosphorylation of the cAMP response element-binding protein transcription factor (CREB), and proinflammatory gene expression such as transcription of IL-6 and IL-8 (39). Using selective blockade of these signaling cascades, Song et al. determined that activation of epithelial IL-6 secretion by *E. coli* might even be faster via the CREB pathway than the canonical pathway and can also be activated by TLR2 and TLR3 ligands (39).

Other TLR pathways important for signalling of innate immunity in response to UTI

Other TLR pathways have been implicated in host defense during UTI. In a recent case-control study of adult women with a history of UTI in which TLR genes were examined,

polymorphisms in TLR1, TLR4, and TLR5 were correlated with protection from, or susceptibility to, some UTI phenotypes (40). TLR2 is stimulated by peptidoglycan, as might be presented by gram-positive uropathogens, including *Enterococcus* and *Staphylococcus* species, as well as by lipoproteins and perhaps OmpA (41) of other extraintestinal pathogenic *E. coli*. Tlr2−/− mice appear to respond normally to acute UTI (31). TLR5 appears to play a UPEC recognition role in the bladder (13). TLR5 recognizes the structural subunit of flagella, which are essential for UPEC motility in the urinary tract induces inflammatory cytokines and chemokines (13). Mice lacking TLR5, which responds to bacterial flagellin, permit higher bacterial loads in the bladder and kidney following transurethral inoculation (13). In contrast to TLR5 which has a bladder-specific role during UTI, TLR11 has a kidney-specific role during UTI (16). The murine receptor TLR11, associated with a pseudogene in humans, also appears to respond to uropathogenic bacteria (16). Conversely, tlr11−/− mice are more susceptible than wild-type mice to UPEC kidney infection (16) a UPEC-encoded homolog has yet to be identified for TLR11 ligand. The fact that there is a stop codon in the open reading frame of human genomic and cell line tlr11 sequences may help explain acute and recurrent UTI susceptibility in humans (16).

Other Non-TLR pathways important for signalling of innate immunity in response to UTI

Surface molecules other than TLRs are also involved in host-UPEC interactions. Upon UPEC exposure, the cytoplasmic tail of uroplakin IIIa undergoes phosphorylation, and intracellular calcium levels increase, presumably important events for uroepithelial cell apoptosis and exfoliation(42) Although uroplakin Ia is thought to be the main receptor for UPEC FimH in vivo (167, 256, 286), type 1 fimbriae may bind to a number of host molecules, including uroplakin complexes (42) extracellular matrix proteins (43) CD molecules (44), and integrins (45). The CD44 ligand, hyaluronic acid (HA), accumulates in the urinary tract during UTI; UPEC can bind HA, thereby facilitating interaction with CD44 and tissue invasion (46). In accordance with this, cd44−/− mice are more resistant to UPEC kidney colonization and successive dissemination (46). Also, there are still unidentified players in inflammation and clearance of UPEC. For example, LPS-responder C3H/OuJ mice were found to be equally susceptible to UTI as non-LPS-responder C3H/HeJ mice yet demonstrated elevated levels of inflammation (47), revealing a susceptibility locus to map.

2.3 Metabolic host pathways against UPEC during UTI

Host factors against iron metabolism of UPEC

That E. coli strains causing UTI have several functionally redundant systems dedicated to iron uptake (48) suggests that the urinary tract, like other host niches, is an iron-limited environment (49). Siderophores are secreted iron-chelating molecules that allow bacteria to scavenge free and host protein-bound iron (50). Enterobactin, for instance, can bind free ferric ions with a higher affinity than transferrin (51) a host iron transport protein responsible for regulating the free iron concentration in serum(52). A transferrin family member, lactoferrin, evokes antimicrobial activity by sequestering iron over a range of pH. Lactoferrin is secreted by kidney cells and is found in neutrophil granules and thus could be involved in combating UTI (53). Both transferrin and lactoferrin have been shown to evoke direct antimicrobial activity by disrupting Gram-negative membranes (54).

In addition to iron sequestration, there are host factors that directly counter the action of siderophores. Early studies indicated that serum albumin, alone or in concert with other

serum proteins, can impede bacterial siderophore function (55). In addition, the mammalian protein lipocalin 2 (Lcn2) can bind and sequester enterobactin and similar catecholate siderophores (56). Lcn2 inhibits enterobactin-dependent propagation of E. coli in vitro, and lcn2−/− mice are unable to control systemic E. coli burdens as well as wild-type mice (56) Production of Lcn2 is induced by TLR4, implicating iron regulation as a part of the immune response to infection(56). Murine GeneChip and quantitative PCR (qPCR) analyses confirmed that Lcn2 mRNA is upregulated by the uroepithelium of infected mice (57). Interestingly, these results were obtained in C3H/HeJ mice, indicating that a TLR4-independent signaling pathway can activate transcription of the lcn2 gene in response to UTI. Not surprisingly, UPEC has evolved a mechanism to counter Lcn2 siderophore sequestration. Encoded within the iroA gene cluster are glycosyltransferases that modify enterobactin in such a way that it cannot be bound by Lcn2 (58). Thus, both the host and UPEC have systems in place to manage their own iron stores and to inhibit iron acquisition by the other—a molecular arms race for an essential nutrient.

2.4 Metabolic host factors against UPEC

The role for bacterial central metabolism during infection has only been recently appreciated (59). Genes important for glucose import were upregulated by the uroepithelium of C3H/HeJ mice experiencing UTI, possibly for either nutrient sequestration or energy to combat infection(57). This fact, coupled with the knowledge that UPEC does not chemotax toward glucose in vitro (60) or utilize glucose as a primary carbon source in vivo (61) implies that UPEC may have evolved to use alternative carbon sources in the urinary tract. These results imply that nutrient acquisition is also a crucial aspect of bacterial pathogenesis and the host response that may influence the outcome of UTI.

2.5 Epithelial host pathways against UPEC during UTI

Life cycle of UPEC in urinary tract epithelium

There has been a growing body of literature revealing that UPEC appears to have three distinct intracellular lifestyle components within the urinary tract (62). The first is uptake by apical endocytosis of Rab27b+/CD63+ fusiform vesicles, which are subsequently recycled back to the cell surface and exocytosed (20). The other two pathways both begin with uptake into a membrane-bound compartment which can lead to either a quiescent nonreplicative existence (63) or escape from compartmental life to undergo a highly replicative phase in the cell cytoplasm. While internalization via the fusiform vesicle pathway may be a side effect of normal bladder epithelium function, cellular uptake by the other two pathways is perhaps intended by UPEC to establish a reservoir to persist in the urinary tract (63). Indeed, UPEC has been shown to exist in the urinary tract for weeks, even after antibiotic treatment (64). Infection of 10 genetically distinct mouse strains also revealed that some strains were more susceptible to persistence than others, indicating that host hereditary components may also contribute to the ability of UPEC to persevere in the urinary tract (65).

2.6 Epithelial host factors have important role against compartmental escape of UPEC

Infected mouse bladder explants monitored by time lapse fluorescence videomicroscopy generated a model for the intracellular UPEC life cycle instigated after uptake in a membrane-bound compartment (nonfusiform vesicle route)(66). While the mechanism of compartmental escape remains undefined, once contained in cytoplasmic “intracellular bacterial communities” (IBCs), UPEC can undergo several changes in morphology,

categorized as early, middle, and late IBC stages (66). Late IBCs that escape exfoliation with umbrella cells contain filamentous UPEC that are not present in C3H/HeJ mice, indicating that this morphological change may be a bacterial stress response to TLR4-mediated immune activation (66). This murine background also experienced increased incidence and severity of IBCs compared to immunocompetent mice (66). Urothelial cells proximal to IBCs in C3H/HeJ mice upregulate transferrin receptor, Lcn2, complement system components (C3, factor B, and CD55), and lysozyme (57). Involucrin and suprabasin transcripts were also increased, indicating that, in addition to gene products that function to eradicate bacteria, proteins important for epithelial integrity may be an imperative host response during UTI (57).

Notably, TLR4 also plays a noninflammatory role in host defense against UPEC by modulating the activity of the observed secretory and vesicular internalization pathways. TLR4-mediated PKA activation suppresses the lipid raft endocytic pathway (21), a possible effort to prevent the establishment of persistence reservoirs. Also along these lines, UPEC exocytosis in fusiform vesicles was actually accelerated by TLR4-mediated recognition of LPS and dependent on the activities of cAMP, Rab27b, caveolin-1, and the scaffolding protein MyRIP (22).

The role of urothelial regeneration in response to UPEC infection

One of the consequences of UPEC infection is exfoliation of the superficial facet cell layer that lines the surface of the bladder lumen (67). Microarray analyses probing regenerative signals revealed that, in addition to genes involved in cell biological processes, inflammatory cytokines, chemokines, signaling molecules, and transcription factors are also upregulated in response to inoculation (68). While regeneration itself appears to be a function of basal stem/progenitor cells in the transitional epithelium (68) studies of the gut epithelium unveiled macrophages as "cellular transceivers" that relay MyD88-dependent inputs from the epithelium to colonic epithelial progenitors via direct contact (69). Whether or not macrophages play a similar role in the urinary tract remains unknown.

2.7 Antimicrobial peptides, cytokines and chemokines against UPEC during UTI

Antimicrobial peptides (AMPs) are short positively charged peptides secreted by both epithelial and hematopoietic cells that disrupt bacterial membranes and can be chemotactic for certain immune cells (70). Human β-defensin-1 mRNA and protein were found in kidney tissue, implicating this AMP in host defense against UPEC (71). More convincingly, mice deficient in defb1, a murine homolog of human β-defensin, have a significantly higher incidence of bacteriuria (72). Murine β-defensin is also a dendritic cell (DC) ligand that instigates upregulation of costimulatory molecules and maturation (73). The human cathelicidin, LL-37, and its murine homolog, cathelin-related antimicrobial peptide (CRAMP), are secreted in response to UPEC exposure (44). Studies using CRAMP-deficient mice revealed that epithelial-derived CRAMP is important during the early stages of UTI while leukocyte-derived CRAMP likely functions later when bacteria penetrate the kidney epithelium (46).

2.8 Cytokines and chemokines against UPEC during UTI

The role of IL-8-mediated neutrophil recruitment in phenotypic susceptibility to UTIs

Human C-X-C ligand 8 (hCXCL8; interleukin-8 [IL-8]) is the main chemoattractant for neutrophils in humans, and murine CXCL1 (mCXCL1) and mCXCL2 (also known as KC

and MIP-2, respectively) are the functional mouse homologs of IL-8 (26). Bladder and kidney cell lines secrete IL-8 in response to UPEC (26). Human and murine studies both demonstrate that neutrophil migration to the UPEC-infected urinary tract is dependent on IL-8 (26). Additionally, mCXCL2 secretion is dependent on TLR4, as secretion was deficient in infected C3H/HeJ mice (100). hCXCR1 and hCXCR2 are receptors for a number of chemokines, including IL-8 (26). Both are expressed in bladder and kidney biopsies, and transmigration studies indicated that hCXCR1 plays a dominant role in IL-8-dependent neutrophil migration (74). Consistent with this, children prone to pyelonephritis tend to have low hCXCR1 expression and heterozygous hCXCR1 polymorphisms (74). Using a large cohort of families that included children with a history of recurrent UTIs, Svanborg and colleagues found that low CXCR1 (IL-8 receptor) expression levels correlated with the incidence of acute pyelonephritis (75). Subsequently, CXCR1 mutations and polymorphisms were identified in several patients with recurrent pyelonephritis (76). Although CXCR1 mutations were not correlated with pyelonephritis in a separate cohort of Italian children, IL-8 gene polymorphisms were found in this latter group (77). hCXCR1 deficiency results in impaired bacterial clearance but, unlike TLR4 deficiency, with intact inflammatory signaling that ultimately results in tissue damage(31).

Similarly, mice lacking mCXCR2 (the functional homolog for hCXCL1) experience subepithelial accumulation of neutrophils, increased bacterial titers, and renal scarring after UPEC inoculation (78) and increased susceptibility to experimental UTI and urinary tract–derived bacteremia (79;80). These data indicate that normal function of neutrophils, their chemotactic ligands, and their chemokine receptors are required for bacterial clearance without postinflammatory sequelae.

The role of other cytokines in phenotypic susceptibility to UTIs

Despite ample information on IL-8 in vitro and in vivo, a complete picture of the cytokine and chemokine dynamics during UTI was lacking. In response, a longitudinal assessment using a Bio-Plex format was conducted(81). Chemokine (C-C motif) ligand 2 (CCL2 or MCP-1), CCL4 (or MIP-1b), CCL5 (or RANTES), CXCL1, IL-1β, IL-6, IL-12p40, IL-17, tumor necrosis factor alpha (TNF-α), and granulocyte-colony stimulating factor (G-CSF) were all upregulated in bladder homogenates from UPEC-infected C57BL/6 mice (81). These results agreed with patient and cell line data regarding upregulation of IL-6 in response to UPEC (82). In mice, TNF-α expression was elevated at 1 h post-inoculation for rapid mobilization of acute responses (81); this waned at later time points, likely to prevent the deleterious effects of uncontrolled TNF-α signaling (16). Expression of most cytokines and chemokines peaked around 24 h post-inoculation, returning to near baseline at 2 weeks (81). These dynamics correlate well with the peak and resolution of bacterial burdens in C57BL/6 mice(81). One notable exception was IL-17, which was highly upregulated from 6 h to 1 week post-inoculation, remaining above baseline through the 2-week experimental duration(81). Importantly, IL-17A (the Th17 signature cytokine) contributes to innate clearance of UPEC through a mechanism involving cytokine and chemokine secretion and macrophage and neutrophil influx (26). Similar to TLR adaptor molecule usage (38) the type of fimbriae expressed also seems to influence the repertoire of chemokines secreted. Specifically, kidney cells exposed to type 1-fimbriated UPEC secrete neutrophil-associated chemokines, while P fimbriae-stimulated cells secrete chemokines targeting antigen-presenting cell (APC)- and Th1-specific cytokines, exemplified by CCL2 and CCL5 expression (83). In addition, IFN-γ and IL-4 (signature cytokines of the Th1 and Th2

lineages, respectively) and IL-10 (a T-regulatory [Treg] effector cytokine) knockout mice were tested for susceptibility to both acute cystitis and pyelonephritis (84). While il4−/− and il10−/− mice appear to experience infection dynamics similar to the wild type, ifnγ−/− mice had increased incidence and severity of UTI (84) implying a role for IFN-γ and Th1-mediated inflammatory responses during UTI.

2.9 The role of neutrophils in immune responses to UPEC-mediated UTI

Infected mouse bladders examined histologically display thickening of epithelium accompanied by robust infiltration of inflammatory cells and edema in the lamina propria (85). Neutrophils are the most rapid and abundant responders to the infected urinary tract (85). Efficient migration of neutrophils requires intracellular adhesion molecule 1 (ICAM-1) expression by epithelial cells and β2 integrin (CD11b/CD18) expression by neutrophils (30). G-CSF is also required for the neutrophil response, and unexpectedly, mice with neutralized G-CSF are more resistant to UTI(81). Although monocyte/macrophage numbers were similar in anti-G-CSF-treated mice, cytokines important for macrophage activation were upregulated, potentially leading to accelerated clearance by enhanced phagocytic killing (81). Despite counterintuitive phenotypes with respect to cytokine knock-down, antibody-mediated knockdown of the neutrophil population confirmed their crucial role in bacterial clearance, especially within the kidney (86). Lastly, the electrostatic properties of the UPEC P fimbrial tip adhesin may interfere with neutrophil binding, a potential host response evasion tactic specific to the kidney (86).

2.10 The role of APCs in immune responses to UPEC-mediated UTI

Compared to the neutrophil response, relatively little is known about APCs in the context of UTI. In mice, resident CD11c+ cells that express low to intermediate levels of F4/80 and CD11b macrophage markers were found in the kidney (87) while CD11c+ cells expressing the major histocompatibility class II activation marker were found in the bladder (30). In spite of macrophage marker expression, CD11c+ kidney cells had physical and functional characteristics of DCs (87). At 24 h post inoculation, CD11c+ cells that migrate to the bladder did not express CD8α, Gr-1, or B220 and thus were not plasmacytoid or lymphoid but appeared to be TNF-α- and inducible NOS (iNOS)-producing (Tip)-DCs (88) that express intermediate levels of CD11b. Infection studies in mice lacking Tip-DCs suggested that they are not necessary for the host response to acute UTI (88). Since Tip-DCs are necessary for the generation of mucosal IgA (89), their role may lie in mediating the humoral response to UPEC. Similar to what was observed for DCs, there appears to be a resident population of macrophages in bladder tissue that increases by several orders of magnitude in response to UTI (81). Monocytes expressing high levels of Gr-1, which can give rise to macrophages or DCs, are also recruited to the bladder in response to UPEC infection. Release of these cells from the bone marrow was dependent on CCR2 (90), and, correspondingly, CCL2 is upregulated in the bladder response to UTI(81).

2.11 The role of the antimicrobial compound nitric oxide (NO) in immune responses to UPEC-mediated UTI

Some of the factors utilized by neutrophils, macrophages, and DCs for pathogen uptake and destruction have been described during UTI. iNOS generates the antimicrobial compound nitric oxide (NO) from l-arginine and was originally reported to be secreted by macrophages

(91). Although iNOS is rapidly upregulated in the inoculated bladder(92) two independent groups reported that inos−/− mice are equally as susceptible to UTI as wild-type mice, suggesting that neuronal NOS, endothelial NOS, or myeloperoxidase may act as compensatory factors (93) Alternatively or in addition, inos−/− animals may lack a colonization phenotype because there are several factors (Hfq and Nsr-regulated genes, polyamines, and flavohemoglobin) expressed by UPEC that enhance tolerance to reactive nitrogen species in vitro (94) suggesting that NO production may be an ineffective host defense against UPEC.

2.12 The role of the complement in immune responses to UPEC-mediated UTI

With respect to the complement system, it appears that UPEC is able to bind C3 to enter host uroepithelial cells via the surface receptors Crry or CD46 (95). Correspondingly, c3−/− mice are more resistant to renal damage and infection (95). As C3 levels are significantly higher in the urine of UTI patients (96) UPEC may stimulate C3 production for pathogenic means or has evolved to exploit this host defense factor.

2.13 The role of innate-like lymphocytes (ILLs) in acute UTI host defense

Infection studies using severe combined immunodeficient (SCID) mice that lack functional B and T cells and nude mice that lack thymically derived T cells provide preliminary evidence of a role for innate-like lymphocytes (ILLs) in acute UTI host defense (97). Epithelial γδ T cells, B-1 cells, and natural killer T (NKT) cells are ILLs: cellular subsets that have relatively invariant receptors and reside in specific locations of the body (26). After a 2-day primary infection, SCID mice had significantly higher bacterial counts in their bladder and kidneys, while nude mice were colonized similarly to wild-type animals (97). The lack of a colonization phenotype in nude mice suggests that either antibody responses independent of thymus-derived T-cell help or extrathymically produced T cells may play a role in innate clearance of UPEC. The latter suggestion has some experimental support.

The role of γδ T cells

γδ T cells can be produced extrathymically and rapidly secrete cytokines in response to stimulation (98). Resident γδ T cells found in the bladder increase in response to UTI (26), and TCR δ−/− mice are more susceptible to UTI than isogenic controls (84). As γδ TCR+ cells express IL-17A during UPEC-mediated UTI (26) this rapid-response cell population may function in concert with other innate factors to mediate neutrophil influx for clearance of UPEC.

The role of B-1 cells

B-1 cells spontaneously secrete large quantities of polyspecific IgM against bacterial and self-antigens, and in contrast to conventional (B-2) B cells, do not require T-cell help (99). While IgM secreted by B-1 cells might play a role in innate clearance of UPEC, current evidence suggests otherwise. JHD mice, lacking both B-1 and B-2 cells (100) infected and monitored over a 14-day time period exhibited no significant increase in incidence or severity of cystitis (84).

The role of NK T cells

On a final note regarding ILLs, administration of α-galactosylceramide (α-GalCer), a ligand for CD1d-restricted NKT cells, alleviates renal UPEC infection (101). Consistent with this, a

resident population of NK1.1+ cells (potentially NK or NKT cells) in the bladder of C57BL/6 mice that increases in response to UTI has been reported (26). Studies using a systemic E. coli infection model suggested that, similar to γδ T cells, NKT cells may act as early amplifiers of the innate immune response to UTI by rapid cytokine secretion (102).

3. Genetic factors that contribute to innate immunity

Although susceptibility to UTI thus far appears to be related primarily to function of the innate immune system, additional determinants are likely important in this polygenic phenotype. For example, the increased susceptibility of C3H/HeJ mice was recently suggested to be due to at least two other loci in addition to *Tlr4 (103)* Accelerating progress in genomic sequencing methodology might facilitate the elucidation of other contributing genes, but these efforts may be hampered somewhat by the continuous, rather than discrete, nature of UTI susceptibility phenotypes in human populations.

The individual's response to UTI is variable and the susceptibility to the infection is inheritable. Lundstedt et al. found in a family study, 15% of the relatives of pyelonephritis-prone children had UTI history, whereas the value was 3% in the controls(75). A evaluation of a familal predisposition about women with recurrent UTI described that 65.5% of mothers, 60.7% of daughters, and 48.6% of sisters of the women had a similar history (104). Many studies discovered that genitic variations of TLR4 and CXCR1 are association with susceptibility to different type of UTIs. And TLR4(896)AG genotype and TLR4(896)G alleles could increase the risk for UTI in childhood (76;105), CXCR1 G (2608) C gene polymorphism and expression are strong linked to acute pyelonephritis in children (77). Reduced expression levels of CXCR1 and TLR4 in neutrophils are associated with pyelonephritis, recurrent cystitis, and asymptomatic bacteriuria in children and premenopausal women (25)(78;106). Although these studies suggest the association of gene polymorphisms and expression of TLR4 and CXCR1 to UTIs, whether the variants are associated with UTI in adults is still unknown.

3.1 Other host factors that contribute to innate immunity

Other mediators also shape the extent of the polymorphonuclear leukocyte (PMN) response to infection. Perpetuation of the PMN response might be controlled by cytokines such as IL-17, which has an emerging role in bridging innate to adaptive immunity(107) and is present at high levels in the bladder at later time points. Plasminogen activator inhibitor type 1 (PAI-1) influences cell migration through its effects on integrin binding; upon UPEC infection of mice lacking PAI-1, kidneys bore significantly higher bacterial burdens and fewer PMN infiltrates than wild-type counterparts did (108). UPEC infection was recently demonstrated to induce the secretion of granulocyte colony-stimulating factor (gCSF) in the bladder, and antibody-mediated depletion of this cytokine reduced PMN influx following UPEC infection (81).

Finally, the secretion of a number of soluble antibacterial compounds into the urinary tract is induced by UPEC infection. UPEC infection also elicits the production of nitric oxide in association with upregulation of the iNOS gene (92). However, UPEC may employ strategies to resist the antibacterial effect of nitric oxide, as mice deficient in iNOS generally have shown no increased susceptibility to UTI (93;109). Among short antibacterial peptides, the human cathelicidin LL-37 is detectable in the urine during human cystitis, and mice deficient in its ortholog (CRAMP) demonstrate increased susceptibility to UTI (110).

4. Cellular and humoral adaptive immune responses to UPEC-mediated UTI

Existing data regarding adaptive immune responses to UPEC are relatively limited. In a seminal study, Thumbikat and colleagues engineered a strain of UPEC to express ovalbumin to examine mechanisms behind antigen-specific adaptive immune responses in experimental UTI (111). In response to reinfection, CD4+ and CD8+ cells infiltrated the bladder and expressed the CD69 activation marker in the spleen (111), extending the findings of early IHC studies probing T- and B-cell populations in infected bladders (109). Furthermore, splenocytes, enriched splenic T cells, or serum antibodies from previously infected donor mice each protected wild-type naïve recipient mice against UPEC challenge (111). This result suggests that protection derived from natural infection is antibody mediated, as UPEC-specific antibody-secreting plasma cells could be present in both splenocyte and enriched T-cell preparations. As expected, transfers from naïve donor mice did not facilitate enhanced protection to recipients (111). This result is in contrast to a previous murine adoptive transfer study where SCID recipients receiving splenocytes from either naïve or vaccinated wild-type donors exhibited equal levels of enhanced clearance, despite the presence of antigen-specific plasma cells in the vaccinated donor cells (97). This result suggests that simply reconstituting immunosuppressed mice with lymphoid cells provides the means (likely stimulatory cytokines for phagocytic cells) for enhanced clearance. Conversely, wild-type recipient mice used in the former study only exhibited enhanced clearance when given cells or serum from antigen-educated, vaccinated donors (111), indicating that enhanced protection in individuals with intact immune systems will be provided only by stimulation of an effective adaptive immune response.

4.1 The role of T cells in adaptive immune responses to UPEC-mediated UTI

T-cell subsets are characterized by transcription factors and cytokines involved in their differentiation and the particular effector cytokines they secrete. To date, studies have not implicated a skew toward Th1- or Th2-mediated UTI immunity (111). DC phagocytosis of infected apoptotic cells is the key event required for DCs to secrete the cytokine milieu necessary for Th17 development (112), and both DCs and infected apoptotic cells are present in the bladder during UTI. Despite this connection, IL-17A is dispensable for the generation of a protective response in a murine reinfection model, suggesting that Th17 cells may not play a role in adaptive responses to UPEC infection (26). Similar to APCs and other lymphocytes, there are resident CD8+ cells in the bladder that increase in response to infection (26;111). It has been suggested that the observed CD8+ cells are either classical cytotoxic T cells or intraepithelial lymphocytes that exert cytotoxic effects on UPEC- or virus-infected cells or rapidly secrete cytokines to mobilize innate immune responses (26). Lastly, the role of Treg subsets in UTI host defense has not been formally examined.

4.2 The role of antibody-mediated clearance in adaptive immune responses to UPEC-mediated UTI

Despite the lack of detail regarding T-cell responses to UTI, there is ample evidence for antibody-mediated clearance of UPEC. The genitourinary tract has been recognized as part of the secretory immune system (113). UPEC-specific antibodies are detected in the urine of infected patients and in the urine or serum of animals exposed to UPEC antigens (111). Urinary IgG and IgA from UTI patients are capable of inhibiting UPEC adherence (114). Patient studies have also suggested that antibody responses to pyelonephritis are, in

general, stronger and last longer than humoral responses to cystitis (115). Analysis of murine urine and serum samples collected before and after vaccination with OMP iron receptors allowed identification of immunological correlates of vaccine-induced protection against UTI (116). Specifically, levels of either urinary IgA or serum IgG (relative to serum IgM; denoted the class switch index) inversely correlated with bladder colonization in vaccinated mice (116). Presumably, urinary IgA plays a direct role in UPEC clearance from the bladder mucosa, while IgG may be a marker for class switching by B cells or also play a direct role in mucosal bacterial clearance. As mentioned earlier, infected JHD mice had wild-type levels of colonization in response to primary infection, suggesting that B cells have no role in innate clearance of UPEC (84). However, this result is not unexpected since both antigen presentation and antibody-mediated protection provided by B cells would likely play a role in adaptive responses, indicating a need for reevaluation of these mice in UPEC reinfection and vaccination challenge models.

5. Immunomodulation as therapeutic option for UTI

There are several practiced and proposed therapeutics for UTI management. Prophylactic treatments include estrogen in postmenopausal women (117) or cranberry juice (118) although the efficacy of the former remains controversial. Immunomodation strategies are emerging therapies for UTIs especially in the setting of increasing antimicrobial resistance.

5.1 Non-vaccine strategies

Since the lining of the urinary tract is highly enriched in TLR4 molecules, administering TLR4 specific ligands directly to the urinary tract could trigger TLR4 mediated innate immune responses thereby enhancing local reactivity and resistance to infection. Treatment of UPEC-infected mice with forskolin, a drug that increases intracellular cyclic AMP (cAMP) levels, expels UPEC from intracellular vesicles into the extracellular milieu, rendering the bacteria susceptible to immune responses and antibiotics (20). Similarly, exposing the bladder to protamine sulfate, a highly cationic protein, removes bound and intracellular UPEC by causing umbrella cells to exfoliate (63)), unfortunately with a significant level of discomfort, as reported by study volunteers (119). In addition to a number of nonspecific chemical treatments (120)), both small-molecule inhibitors (121) and specific antibody directed against FimH (122) demonstrated some utility in preventing bacterial adherence. While antibiotic therapy remains the standard treatment for UTI, overuse leads to deleterious alterations of the normal host microbiota (123) and selection for resistant strains (124), prompting the need for vaccine-mediated prevention of UTI.

Astragalus is a Chinese herbal medicine, and Astragalus polysaccharide (APS) is its main components. Previous studies have demonstrated that APS could induce enhancement of expression of TLR4 on bladder epithelial cells (125) and astragalus also increases the TLR4 expression on monocytes in UTI patients. These suggest that similar to LPS, APS can activate pre-inflammatory factor secretion during the early stages of infection similar to LPS, promote TLR4 expression, and involve mucosal innate immunity of the urinary tract. However it remains to be seen whether this herbal medicine can be a therapeutic option for UTI.

These observations suggest that activators of the TLR4 signalling pathway in the urinary tract can be effective therapeutic agents against infections. Furthermore, it is not necessary

to use TLR4 ligands for activation of the pathway. Inducers of downstream substrates of the pathway are also effective activators of the innate immune response. Even if TLR4 ligands are employed for therapeutic use, it is unlikely that LPS will be the ligand of choice since LPS has intrinsic toxicity. A TLR4 ligand with greatly improved safety profiles, such as monophosphoryl lipid (MPL), could be used in its place (126).

5.2 Vaccines

The involvement of TLRs in the immune response to UTI and current knowledge of their ability to incite innate and direct adaptive responses make them attractive adjuvant candidates for UTI vaccines (127). These and other mucosal adjuvants and variations in vaccination routes and schedules must be tested in an effort to generate UPEC-specific local and systemic antibodies(128) and optimize production of immunological memory, not tolerance . A more detailed knowledge of adaptive immune responses to UPEC is a prerequisite for the development of next-generation candidate vaccines for the prevention of UTI. More recently, a variety of experimental approaches have been applied to search for immunodominant epitopes, revealing an array of new candidate targets, and thus a number of vaccine antigens have been explored (26).

Lipopolysaccharide (LPS) and side chain (O) antigen as vaccine targets

Early vaccine studies focused on the lipopolysaccharide (LPS) side chain (O) antigen (129). There are trends regarding the frequencies of particular O antigens among UTI isolates(130) and O-antigen-specific antibodies demonstrate an anti-adhesive effect (130). Nonetheless, significant structural heterogeneity may represent an insurmountable obstacle for development of an O-antigen-based vaccine. Furthermore, a study evaluating antibody responses in mice intranasally vaccinated with a killed *E. coli* lacking capsule and O antigen demonstrated that these surface features actually obstruct optimal humoral responses (131)

P fimbriae as vaccine targets

Later studies involved vaccines directed against particular virulence factors. The pore-forming toxin alpha-hemolysin (HlyA) and P fimbriae are proposed minimal factors required for colonization of and dissemination from the kidney (132). P fimbriae are adherence organelles that play a role in kidney colonization in mice and humans (133). There are convincing data using both murine (132) and primate models (134) that vaccination against P fimbriae or HlyA prevents renal colonization and damage. Additionally, to overcome P fimbrial allelic variability, linear peptide sequences that generated cross-reactive antibodies were evaluated as protective antigens (135). Despite these successes, vaccines targeting P fimbriae may not be effective because of their limited role during bladder colonization. Type 1 fimbria is a *bona fide* virulence factor of UPEC and, in contrast to P fimbria, is critical for bladder colonization (136). Animals vaccinated with various components of type 1 fimbriae had increased levels of antigen-specific antibodies and decreased levels of colonization upon challenge (137). Unfortunately, expression of type 1 fimbria is subject to phase variation, allowing UPEC to evade humoral responses targeting this organelle(138). Additionally, since nonpathogenic isolates also express type 1 fimbriae (139), targeting this population may result in detrimental disruption of the host microbiota. Also of note, both P and type 1 fimbriae were not necessary for colonization of the human neurogenic bladder, indicating the need for alternative targets in certain high-risk patient groups (140). Although vaccines based on P or type 1 pilus components have generated

substantial mucosal antibody responses, protection from subsequent infections has been incomplete, perhaps because of phase variation in the expression of these antigens during infection.

Iron pathway as target for vaccine

Iron is essential for nearly all organisms (141) and UPEC strains encode a battery of genes involved in iron acquisition. Vaccination with UPEC outer membrane protein (OMP) fractions enriched for iron receptors protects against experimental sepsis (142). Additionally, mice vaccinated subcutaneously with denatured IroN, an OMP siderophore receptor and urovirulence factor (143), had both increased levels of antigen-specific serum IgG and reduced kidney colonization upon challenge (144). Undetectable levels of IgA in the bladder mucosa after this vaccination may explain why these animals were not protected from cystitis (144). Recently, a broad functional vaccinology initiative was conducted using an "omics" approach to identify vaccine candidates: UPEC proteins that are pathogen-specific, antigenic, surface-exposed, and *in vivo* expressed (26). Strikingly, the top targets identified by this approach were all OMPs functioning in iron uptake. Intranasal vaccination with three of six candidates afforded protection from cystitis and pyelonephritis, suggesting that combining antigenic motifs found in these proteins may be an effective multivalent vaccine for UTI (26).

Other vaccine targets

Vaccines consisting of bacterial components or whole cells have also been assessed. Transurethral immunization of mice with a live-attenuated UPEC strain lacking the ability to persist in the urinary tract engendered heterologous protection (145) a potential platform for further development. SolcoUrovac, a vaginal suppository containing 10 heat-killed uropathogenic strains, has been tested in mice , in nonhuman primates , and in clinical trials (26). While safe, SolcoUrovac vaccination did not result in appreciable increases in local specific antibody, nor did it afford protection without periodic readministration (146).

Vaccine strategies to combat UTIs

Since B and T cells, which mediate adaptive immunity are critically dependent on signals derived from the innate immune system, modulators that boost innate immune responses may be of value in boosting adaptive immune responses (147-150). Thus, immunomodulators used to boost innate immune responses in the urinary tract may be also employed to boost adaptive immune responses. One of the reasons for administering vaccine antigens against UTIs in the genitourinary tract, as in the case of the vaginal mucosal vaccine mentioned above, is to evoke secretory IgA (sIgA) antibodies in the mucosal surfaces of the urinary tract. Whereas subcutaneous, intramuscular, or intravenous immunization evokes strong systemic IgG responses to the vaccine antigens, they fail to evoke IgA antibodies in the mucosal surfaces of the urinary tract where infections are initiated and where antibodies are most needed (111).

However, administering vaccines directly to the urinary tract is neither easy nor practical. A much more accessible mucosal site for the delivery of vaccines is the nasal passages. Delivery of proteus antigens into the nasal passages of mice have been shown to evoke high levels of sIgA in the urine and this was accompanied by impressive protection against *Proteus mirabilis* induced UTI (151). Immunization at nasal sites has been shown to be highly effective in evoking antigen specific serum IgG as well as sIgA responses in various mucosal

sites presumably due to activation of the nasal associated lymphoid tissue (NALT) found in the nasal passage. Since the NALT is a potent immunologically inductive and sampling site, it can respond vigorously to vaccine antigens and if TLR ligands or other adjuvants are present, this response may be even more magnified (152). Taken together, an alternate or complementary approach for the management of UTIs in the future could be targeted administration of modulators of the TLR signalling pathway to boost both innate and adaptive responses in the urinary tract.

Cumulatively, all the indications suggest that the urinary tract is able to mount an appreciable and protective adaptive immune response and that this property can be harnessed for vaccination purposes. An important and as yet unanswered question is the duration of protection in the urinary tract following infection or vaccination. Since up to 25% of women with UTIs that have no underlying immune competency issues have recurrences (153) it is conceivable that the immunity generated in the urinary tract could be relatively short lived and therefore frequent vaccinations may be required.

6. Conclusion

The over use of broad spectrum antibiotics has led to the emergence of antibiotic resistant bacteria many of which have been implicated in UTIs. As a consequence, management of these infections constitutes a serious and growing medical challenge. Modulating or co-opting the powerful innate and adaptive immune systems of the urinary tract could potentially have important therapeutic and prophylactic implications for the treatment of UTIs, particularly where conventional approaches are ineffective.

There is considerable work to be done to better understand the mechanisms of protective immunity against UPEC in the bladder. Specifically, available knockout mouse strains could be used to systematically evaluate the role of various receptors, signaling molecules, cytokines and chemokines, and cell types in controlling UPEC-mediated UTI and eliciting potent adaptive and memory immune responses. Ideally, the field can acquire insights on UTI immunity at a level suitable to rationally develop a much-needed vaccine that elicits sterilizing immunity against UPEC in the human urinary tract.

Unlike antibiotic treatment, immunomodulation will not be broadly applicable. Instead, it will have to be tailored to each patient and must take into consideration, among other factors, the virulence and antibiotic resistance profile of the infecting bacteria as well as the age, immune competence and genetic make-up of the patient. For example, employing TLR4 ligands to boost immunity in patients with defective TLR4 genes will not be productive but the use of activators of downstream components of the pathway could be useful. Thus, for these proposed emerging strategies to be completely effective, comprehensive information regarding relevant traits of the pathogen and the host will become necessary.

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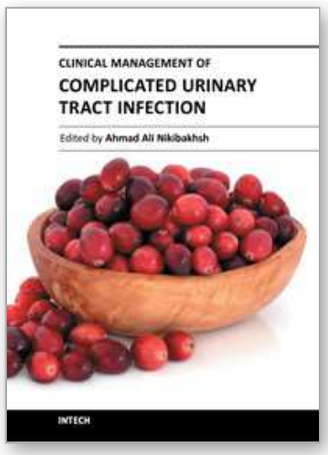

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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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