Ablation of the Tamm-Horsfall protein gene increases susceptibility of mice to bladder colonization by type 1-fimbriated *Escherichia coli*

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**URINARY TRACT INFECTIONS (UTIs)** are the second most common infectious disease, occurring about 150 million times annually on a global basis and costing over $6 billion in health care expense (48). One in five UTI episodes may be followed by a recurrent UTI episode, causing considerable morbidity and time lost from work. Recurring UTIs increase the risk for pyelonephritis and long-term renal damage. The emergence of drug-resistant uropathogens presents a further clinical challenge (4).

Great strides have recently been made in understanding UTI pathogenesis, the most significant of which is the revelation of the molecular players at the pathogen-host interface (33, 36, 58, 70). To cause infection, uropathogenic *Escherichia coli*, by far the most common cause of UTI, must first adhere to the bladder epithelial surface (15, 49, 65). The adhesion allows the *E. coli* to gain a foothold in the bladder and thereby prevents complete expulsion of the bacteria during micturition. Of the many adhesins produced by *E. coli*, the FimH lectin of type 1 fimbriae appears to be the one most critical for establishment of cystitis (6, 10, 27). In vitro and in vivo animal studies demonstrated that FimH can bind specifically to the mannosylated uropelakin Ia receptors present on the urothelial surface (32, 34, 68, 70, 71). The adhesin/receptor binding is essential to triggering the internalization of the *E. coli* into the superficial (umbrella) cells of the urothelium (29, 34). Once inside these cells, the *E. coli* propagates rapidly, culminating in the destruction of the host epithelial cells and the activation of a cascade of host inflammatory responses. Therefore, mounting experimental evidence indicates that the interaction between the *E. coli* adhesin and its urothelial receptors plays a critical role in the initiation of UTI.

Despite this progress in our understanding of adhesin-receptor interactions in the urinary tract, little is known about the innate host defenses that naturally counter bacterial adhesion. In the respiratory and intestinal tracts, much of the anti-adherence activity is tied to the abundant mucus secretions that effectively shield the epithelial receptors from the invading pathogens (26, 31, 55, 67). However, several recent high-resolution electron microscopic studies suggest that such a conspicuous mucus protection is absent from most, if not all, of the urothelial surface (22, 34, 68). Indeed, the uroplakin receptors for the FimH adhesin can be seen directly exposed to the urinary space. To prevent uropathogen adhesion to the urothelial surface, the urinary system must therefore rely on the physical cleansing effects imparted by micturition and, perhaps as importantly, the soluble anti-adhesion factors present in the urine. A prominent candidate for an anti-adhesive urinary factor is the Tamm-Horsfall protein (THP), or uromodulin. THP is the most abundant protein in mammalian urine, with an excretion rate of up to 100 mg daily (24, 25). Made by the tubular cells of the ascending limb of Henle’s loop of the kidney, THP is anchored onto the apical membrane via glycosphatidyl inositol linkage and is released into the urine by the activity of either proteases or phospholipases (5, 11, 12, 17, 40, 45). THP has a tendency to self-aggregate via its juxtamembrane-positioned zona pellucida domain, forming filament-like polymers (20), a characteristic potentially important for trapping of *E. coli*. Although the physiological function of THP is unknown, several lines of evidence suggest that THP...
may play a role in host defense. First, THP contains high mannose residues that are capable of interacting with the FimH adhesins (7, 38, 39, 42, 51). Both THP and its high mannose moieties are well conserved across species, suggesting an indispensable role during evolution (38, 53, 56). Second, type 1-fimbriated E. coli were found to be trapped within the renal cast primarily consisting of THP (37). Third, type 1-fimbriated E. coli can bind to immobilized THP in vitro (16), and this binding blocked the binding of E. coli to kidney epithelial cells (28). Finally, our recent in vitro adherence studies showed that soluble THP binds to type 1-fimbriated E. coli and competitively inhibits the E. coli from binding to the immobilized UPIa receptors (38). These studies, therefore, suggest a putative role for THP as a competitive inhibitor of the FimH adhesin of the type 1-fimbriated E. coli. Whether THP is important in innate urinary defense in vivo, however, is still unclear and is the subject of the present study.

MATERIALS AND METHODS

THP gene targeting. A 60-kb DNA fragment was isolated from a 129/SvJ mouse genomic (BAC) library by PCR-based mass screening using THP-specific oligonucleotide primers (72). Southern blotting with probes located in the 5'-end, middle region and 3'-end of the mouse THP cDNA confirmed that the genomic fragment contained all coding regions plus 5'- and 3'-noncoding regions. A 3.1-kb XbaI/SpeI restriction fragment in the 5'-upstream region of the THP gene was subcloned into pBluescript, retrieved by XbaI digestion, and cloned into the XbaI site that was 5' to the Neo gene in the pLOXPN T targeting vector (21). A 2.5-kb EcoRI/SacI fragment (containing partial intron 4, exon 5, intron 5, exon 6, and partial intron 6) of the THP gene was subcloned into pBluescript, retrieved by EcoRI digestion, and cloned into the EcoRI site between the Neo and the TK genes in the targeting vector. The vector was linearized by XhoI and was introduced by electroporation into 129/SvEv (W4) embryonic cell line. After transfected cells were double-selected in 200 μg/ml G418 and 2 μM ganciclovir, Southern blotting was used to identify ES cell clones with the correct homologous recombination event. Two ES cell lines (designated as A2 and C12) that were heterozygous for the targeted deletion were microinjected into blastocyst-stage embryos derived from C57BL/6J mice. The injected blastocysts were transferred into the uterus of pseudopregnant C57BL/6J mice. Of the 32 chimeric mice obtained (14 from A2; 18 from C12), 22 male chimeras were bred with Black Swiss mice and all of them transmitted the mutant allele to their offspring. Male chimeras were also bred with 129/SvEv inbred mice to generate heterozygous mice, the latter of which were used to generate homozygous mice. The genotype of the offspring was determined by Southern blotting of EcoRI-digested tail DNA (Fig. 1). All animal studies were conducted in conformity with American Physiological Society’s Guiding Principles for the Care and Use of Animals and based on a protocol approved by investigators’ institutions’ Institutional Animal Care and Use Committees.

RNA and protein analyses. Total RNA was extracted from mouse kidneys using an RNA extraction kit (Promega). For RT-PCR analysis, 2 μg of the total RNA were reverse-transcribed and one-tenth of the transcribed product was PCR-amplified with a pair of primers located in exon 3 of the mouse THP gene (forward: 5'-AGGGCTTTACAGGGGATGGTTG-3'; reverse: 5'-GATTGCACCTCAGGGGGCTCTGT-3'). PCR conditions were as follows: 95°C for 5'; 95°C for 30', 58°C for 30', 72°C for 1' for 40 cycles; and 95°C for 30', 58°C for 30', 72°C for 8' for the last cycle. Glyceraldehyde-6-

Fig. 1. Generation of Tamm-Horsfall protein (THP)-deficient mice by targeted deletion of the THP gene. A: targeting strategy. Exons of the mouse THP gene are indicated with filled boxes (1–11), and 5'-upstream region and introns are indicated with thick lines (top). The targeting vector (middle) contained a 3.1-kb 5'-upstream region of the THP gene, a Neo-resistance (Neo) gene, a 2.5-kb THP fragment (spanning partial intron 4, exon 5, intron 5, exon 6, and partial intron 6), and a thymidine kinase (TK) gene. Homologous recombination would introduce a Neo gene in the targeted THP locus and delete a 650-bp proximal promoter region, exons 1–4, introns 1–3, and partial intron 4 (bottom). A 5'-probe (probe) was designed to detect a 7.0-kb wild-type (WT) allele and an 8.5-kb mutant [knockout (KO)] allele. Restrictions sites are E, EcoRI; X, XbaI; S, SpeI; Sa, SacI; and N, NcoI. B: genotyping of THP-mutant mice by Southern blot analysis. +/+; WT; +/-, heterozygotes; −/−, homozygotes (KO). C: RT-PCR analysis of THP expression in mouse kidneys. Top: note the absence of THP in homozygous mice. Bottom: GAPDH was used to illustrate the integrity of mRNA. D: Northern blot analysis. Total RNAs (15 μg) resolved by agarose gel (middle) were hybridized with a full-length mouse THP cDNA probe (top) followed by a β-actin probe (bottom). Note the reduced expression of THP in +/− mice and absence of THP in −/− mice.
phosphate dehydrogenase was used as an internal control. For Northern blot analysis, 15 µg of the total RNA were resolved by formaldehyde-agarose gel, transferred onto a nylon membrane, and hybridized with a mouse THP cDNA probe. After autoradiography, the probe was stripped by high-stringency washing and the nylon membrane was rehybridized with a β-actin probe.

For the assessment of urinary THP status, mouse urine was collected following suprapubic massage and immediately denatured in SDS-PAGE-loading buffer containing 2% SDS, 5% mercaptoethanol, and 50 mM Tris-HCl (pH 6.8). Total urinary proteins were resolved on an 8% SDS-PAGE and were either stained by Coomassie Blue to reveal the total proteins or transferred onto an Immobilon-PVDF membrane for Western blotting using a polyclonal antibody raised against human THP (Biodesign International). The reaction was visualized by a secondary antibody conjugated with horseradish peroxidase followed by development using an enhanced chemiluminescence detection system (Amersham).

Histology and immunohistochemistry. Freshly dissected kidney tissues were fixed in 10% buffered formalin and processed routinely for paraffin embedding. Three-micron tissue sections were stained with hematoxylin/eosin and examined by light microscopy. Alternatively, the sections were microwaved in a citrate buffer (pH 6.0) for 15 min for antigen retrieval and stained with the anti-THP antibody.

RESULTS

Targeted ablation of the mouse THP gene. Germline inactivation of the mouse THP gene was carried out using a replacement targeting vector whose homologous recombination with the endogenous THP gene would delete not only the first four exons, but also a 650-bp proximal promoter region of the THP gene, thus rendering the THP gene nonfunctional (Fig. 1A). Of the 132 ES cell clones that were resistant to both G418 and ganciclovir, two clones (designated A2 and C12) had the correct homologous recombination event in one allele of the THP gene. Microinjection of the two clones into the blastocysts derived from C57/BL6J mice and implantation of these blastocysts into the uteri of C57/BL6J mice resulted in the birth of 32 chimeras. All 22 male chimeras showed germline transmission of the mutated THP allele, and they were bred with 129/SvEv females to generate heterozygotes (Fig. 1B). Further breeding of heterozygotes yielded offspring with anticipated litter size and with different genotypes (THP+/+, THP+/−, and THP−/−; Fig. 1B) distributed in a Mendelian fashion. This indicated that THP gene deletion did not adversely affect embryonic development.

To determine whether the THP gene was indeed inactivated in the knockout mice, we assessed THP expression on both mRNA and protein levels. RT-PCR using primers located within exon 3 of the mouse THP gene detected a specific product in wild-type and heterozygous mice, but not in homozygous mice (Fig. 1C). Similarly, a full-length mouse THP cDNA probe failed to detect any THP mRNA on a Northern blot using RNA from homozygous mice (Fig. 1D). Immunohistochemical results using a polyclonal anti-THP antibody demonstrated strong labeling in wild-type animals in the thick ascending limb of the Henle’s loop and early distal tubules (Fig. 2A), renal tubules known to synthesize THP (9, 54). The labeling was confined to the luminal surface of the tubules, consistent with the fact that THP is normally anchored onto the apical leaflet of the plasma membrane via GPI linkage (Fig. 2A; Ref. 45). Heterozygous mice stained less strongly for the anti-THP antibody (Fig. 2B), whereas homozygous mice were completely negative (Fig. 2C). Because THP is known to be present in normal urine in large quantities (24, 25), we performed Western blot analysis using the polyclonal anti-THP antibody. The 100-kDa THP protein species was present in wild-type and heterozygous mice but was absent in homozygous mice (Fig. 2, D and E). Taken together, these results firmly established the complete inactivation of THP gene expression in the knockout mice.

THP deficiency predisposes mice to bladder infection. To examine the potential role of THP in protecting against urinary bladder infections, we inoculated the bladders of THP-deficient and wild-type mice with isogenic E. coli strains that varied in their expression of two adhesins that have been shown to be important in establishing UTIs, type 1 and P fimbriae. Type 1 fimbriae are hairlike structures composed primarily of the structural subunit FimA and exhibiting a mannose-sensitive lectin subunit FimH at the fimbrial tips. The two recombinant type 1-fimbriated strains expressed fimH bearing either a urapathogenic fimH allele or a mutated, nonfunctional fimH (38, 58). Twenty-four hours after transurethral inoculation, the FimH-negative mutant (KB18) was not present in the bladders of either mouse group, even at an inoculum of 10⁸ E. coli (Fig.
THP and Urinary Defense

3A), whereas the strain expressing a functional FimH adhesin (KB96) effectively colonized the bladders of both wild-type and knockout mice. This result indicated that E. coli colonization was strictly FimH dependent and that high numbers of bacteria could effectively overcome host defenses (38, 58). However, significant differences were observed when lower numbers of E. coli were inoculated. For example, at an inoculum of $10^5$ E. coli, 65% (11/17) of the bladders of the knockout mice were colonized, compared with 24% of the wild-type mice ($P < 0.05$; Fig. 3B), and even with an inoculum of $10^4$ E. coli, 55% of the bladders of knockout mice were colonized, compared with only 5% of the wild-type mice ($P < 0.01$). Furthermore, larger numbers of E. coli could usually be recovered from the bladders of knockout mice than wild-type mice (Fig. 3C). Similar results were obtained with a clinical UTI strain (MJ35) that expressed the type 1 fimbriae (Fig. 3D). The greater level of colonization in knockout mice could also be seen when tissue sections were examined for E. coli by immunofluorescence (Fig. 4, B and C). Thus, under normal circumstances, in which the urinary tract would most likely be exposed to relatively small numbers of pathogenic E. coli, THP plays a critical role in the first line of defense, presumably by saturating the FimH adhesins, inhibiting their binding to urothelial cells and, thereby, facilitating the pathogen’s elimination.

Parallel experiments in which the bladders were inoculated with E. coli strains expressing P-fimbriae failed to show any effect of THP absence on E. coli colonization (Fig. 5). This observation is consistent with the fact that P-fimbriae appear to be dispensable for bladder colonization (69), and it clearly indicates that the protective role afforded by THP against bacterial infection is type 1 fimbria specific. Whether THP deficiency could predispose bladder colonization by other strains of P-fimbriated E. coli remains to be determined.

Discussion

Unlike the intestinal tract, which is well populated by E. coli and many other species of bacteria, the urinary tract is normally sterile (18, 23). This sterility is usually maintained despite the fact that the urinary tract is steadily exposed to numerous intestinal pathogens by virtue of the anatomic proximity of the urinary and intestinal orifices and the fact that the uroplakin receptors are directly exposed to the urinary space and readily accessible to E. coli type 1 fimbriae (22, 34). The ability of the urinary tract to ward off the invading pathogens has long been attributed to the voiding action of the bladder (46). In addition, it was recently discovered in an experimental mouse model that the urothelium could defend against the E. coli by shedding off luminal cells that had become apoptotic following E. coli attachment and invasion (34). By abating the THP gene, we provide the first in vivo evidence indicating that the urinary tract possesses yet another crucial defense mechanism involving THP. We demonstrated that intravesicular inoculation of type 1-fimbriated E. coli caused significantly greater bladder colonization in mice lacking THP than the normal controls (Figs. 3 and 4). This result, combined with our recent observation that purified THP can bind to type 1-fimbriated E. coli and prevent them from binding to the uroplakins (38), strongly suggests that THP can serve as an innate defense, preventing E. coli binding to the urothelial surface. It should be noted that intravesicular inoculation of large numbers of E. coli (ranging from $10^7$ to $10^{10}$) could cause bladder colonization/infection even in wild-type mice as shown in our present study and many other previous studies (6, 14, 35, 58, 60). However, these large inocula may not be physiological because they likely exceed by several orders of magnitude the number of E. coli that would initially invade the urinary tract under most circumstances. Therefore, under physiological conditions where a small number of E. coli invades the urinary tract, the...
amount of urinary THP would likely be sufficient to overwhelm the invading pathogens.

Based on our recent understanding of UTI pathogenesis, it can be proposed that THP exerts its defensive role by acting as a competitive inhibitor of the interaction of the FimH lectin adhesin with urothelial receptors. Using an in vitro adhesion system, we previously showed that type 1-fimbriated E. coli can bind to highly purified urothelial plaques that cover over 90% of the bladder surface (70). This binding can be abolished by D-mannose suggesting that it is mediated by the mannosylated glycoproteins of the urothelial plaques. A gel-overlay assay established that E. coli specifically recognized UPIa and UPIb but not their deglycosylated forms lacking the high mannoses, strongly indicating that the urothelial binding by the type 1-fimbriated E. coli was mediated by the FimH adhesin of the E. coli and the mannose receptors of the uroplakins (70). The fact that the binding can be reproduced with urothelial plaques purified from human, monkey, cattle, and mice suggests that the high mannose modification of the uroplakin I’s is highly species conserved (70). Our in vitro results were recently corroborated structurally by an in vivo infection model in which the tip of the type 1 fimbriae was seen to interact directly with the center of the uroplakin particles where UPIa and UPIb are likely to be situated (32, 34). Finally, both in vitro and in vivo experiments showed that allelic variants of type 1-fimbriated E. coli prevalent in UTIs, rather than those prevalent in feces, bind to uroplakins and cause more bladder colonization (58). This suggests that FimH-uroplakin interaction provides a selective advantage for certain intestinal E. coli to survive in the urinary tract. These studies established the role of uroplakins as the “immobile” urothelial receptors for the type 1-fimbriated E. coli.

As a competitive inhibitor preventing FimH adhesin from binding to the uroplakin receptors, THP possesses several
E. coli staining of the bladder nuclei (red). Fluorescent microscopy showed little to no
adherence (green; arrows) with an anti-E. coli antibody (green) followed by propidium
iodide counterstaining of the bladder nuclei (red). Fluorescent microscopy showed little to no
E. coli adhesion in WT mice (A) and a large number of E. coli (green; arrows) adhering to the
urothelial surface in homozygous mice (B). Both panels are ×400. C: hematoxylin and eosin staining showing internalized E. coli in a
superficial umbrella cell (arrows; ×1,000).

It should be noted that the bladder colonization experiments described here are of a short-term nature. Long-term experiments should tell us whether THP deficiency also plays a role in the pathogenesis of chronic and recurrent bladder infections.

THP abnormalities, both quantitative and qualitative, have been associated with several pathological conditions in humans. A notable example is type I diabetes, in which patients have a profound reduction in urinary THP (1, 2, 62, 63). Diabetes is also frequently associated with an abnormal glycosylation pattern of the urinary proteins including the THP (8, 41, 61). It is therefore of particular interest to note that diabetic patients are extremely prone to UTIs, perhaps due to altered and reduced THP (13, 19, 47). Although diabetic patients also have granulocyte dysfunction, which could render a host more susceptible to UTIs, Langermann and co-workers (27) demonstrated that FimC/H vaccine was equally effective in protecting the bladder against infection by the type 1-fimbriated E. coli in both neutropenic and nonneutropenic mice. This suggests that THP dysfunction can contribute significantly to the propensity of diabetic patients to developing UTIs, independent of the neutrophil status. Urinary THP reduction has also been found in acute tubular necrosis, hyperprostaglandin E syndrome, and active lupus nephritis (30, 50, 64). The consequence of such a THP reduction in these pathological conditions, however, remains to be elucidated. Thus far, only a few studies have been attempted to correlate THP with human UTIs. In two separate studies, Reinhart and co-workers (43, 44) found that the concentrations of aggregated THP were dramatically decreased in

Fig. 4. Morphological identification of E. coli bound to the urothelial surface.
Twenty-four hours after mice were transurethrally challenged with 10⁴ E. coli,
the bladders were excised, fixed, and subjected to immunofluorescent staining
with an anti-E. coli antibody (green) followed by propidium iodide counter-
staining of the bladder nuclei (red). Fluorescent microscopy showed little to no
E. coli adhesion in WT mice (A) and a large number of E. coli (green; arrows)
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important properties. THP is present in all placental mammals
(24, 25) and is synthesized by the renal tubular cells and
excreted exclusively in the urine with a concentration reaching
0.1 mg/ml. It is conserved across species not only in its primary
structure but also its high mannose moieties. Thus the high
mannose glycosylation has been found in all species examined
including murine, bovine, porcine, and human (38, 53, 56). The
glycosylation of THP is so persistent that, even when trans-
fected and expressed in cultured cells originally not synthesiz-
ing the THP, THP is still modified by the high mannoses (52).
It has therefore been suggested that THP’s high mannose
glycosylation is determined by the fundamental protein struc-
ture and unique folding of the peptides surrounding the glyco-
sylation site. Van Rooijen and co-workers (66) recently
mapped the glycosylation site to Asn 251 in human THP.
Using thin-layer chromatography and later ¹H NMR spectros-
copy, Serafini-Cessi and colleagues (7, 51) established that
native human THP bears predominantly the Man₅₋GlcNAc₂
high mannose type (73 vs. 19% Man₇₋GlcNAc₂ and 8% Man₄₋GlcNAc₂). Consistent with the structural data proving the
existence of high mannoses in THP, type 1-fimbriated E. coli
were found to bind in a mannose-specific fashion to highly
purified THP (38). Given the large amounts of THP in the
urine, the binding between THP and type 1 fimbriae can potentially saturate the adhesins of E. coli, thereby preventing
the latter from binding to the uroplakin receptors. The major
advantage of this type of defense mechanism is that it prevents
E. coli from adhering to urothelial cells, thereby averting the
serious consequences that follow adhesion.

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THP reduction in these pathological conditions, however, remains
to be elucidated. Thus far, only a few studies have been
attempted to correlate THP with human UTIs. In two separate
studies, Reinhart and co-workers (43, 44) found that the
concentrations of aggregated THP were dramatically decreased in

Fig. 5. THP absence did not increase bladder colonization by P-fimbriated E.
coli. WT and mutant mice (7 mice/group) were challenged transurethrally with
nonfimbriated negative controls [KB18 (ΔfimH) and P678–54], a type 1-fimbriated-positive control (KB96) or P-fimbriated strains
(HU849 expressing PapG1 adhesin and IA2 expressing PapG2 adhesin). Although larger numbers of KB96 colonized the bladders of THP-KO mice than the WT mice (P < 0.01; Student’s t-test), neither P-fimbriated E. coli strain showed any enhanced colonization in the mutant mice, suggesting that urinary defense provided by
THP is type 1 fimbria specific.
children as well as in the elderly during the episodes of UTI. Despite a demonstrated correlation in these reports, more studies are clearly needed to establish a role for THP in human UTIs. It is well known that the majority of recurrent UTIs occur in anatomically normal individuals. We speculate that physiological defects in the components of innate urinary defenses, such as THP, may account for the predisposition of some individuals to recurrent UTIs.

In summary, we showed by a gene-knockout approach that THP deficiency can lead to increased bladder colonization by type 1-fimbriated E. coli. Our results indicate that THP can serve as an effective defense factor in the urinary tract by competitively inhibiting the FimH adhesin from binding to the uroplakin receptors. Because quantitative and qualitative defects of THP are known to exist in humans, it will be extremely interesting to determine whether these defects are the underlying causes of some of the UTIs, particularly recurrent UTIs in humans. Finally, THP has been proposed to play roles in physiological defects in the components of innate urinary defenses, such as THP, may account for the predisposition of some individuals to recurrent UTIs.
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