Recent advances into the pathogenesis of recurrent urinary tract infections: the bladder as a reservoir for uropathogenic *Escherichia coli*

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Abstract

Recurrent cystitis is a common clinical entity that is becoming increasingly challenging to manage. The current thought regarding the pathogenesis of these infections is evolving as new data emerges to suggest that some recurrences may originate from previously unrecognized reservoirs of uropathogenic *Escherichia coli*. This article will summarize recent conceptual changes with respect to the aetiology of recurrent urinary tract infections, particularly as it relates to chronic bacterial persistence in the bladder. © 2002 Elsevier Science B.V. and International Society of Chemotherapy. All rights reserved.

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1. Introduction

Urinary tract infections (UTIs) are one of the most common infectious diseases in the USA [1]. The majority of UTIs that occur in the community are caused by uropathogenic *Escherichia coli* (UPEC). Acute UTIs are associated with substantial morbidity and this is made worse by high likelihood of recurrent infections. Up to 25% of women who have a first UTI will have a second infection within 6 months [2]. Despite the clinical significance of recurrent UTIs, several questions remain regarding the pathogenesis and treatment of these infections.

It is generally accepted that recurrent UTIs are the result of UPEC migrating from the gastro-intestinal tract (GIT) to the periurethral area, and eventually up the urethra and into the bladder [3]. Consistent with this model, UPEC can be detected in faecal samples of women who subsequently have a UTI with that same strain of *E. coli* [4]. Furthermore, women who suffer from recurrent UTIs have a higher frequency and magnitude of vaginal colonization with *E. coli* compared with women who have never had a UTI [5]. Cultured vaginal epithelial cells from women with recurrent UTIs have also been shown to support higher levels of bacterial adherence, potentially explaining the higher levels of vaginal colonization in these women [6]. However, the application of antibiotic ointment to the periurethral area does not significantly reduce the risk of UTI recurrence [7].

Furthermore, the presence of uropathogens in the GIT or vaginal area is not associated with an increased risk of UTI recurrence [8,9]. These data suggest that additional factors and/or alternate mechanisms may also contribute to recurrences in the urinary tract (UT). Notably, a high percentage of recurrent infections are caused by the same strain of UPEC that had been isolated from the original UTI [4,10–13]. Importantly, this is not a consequence of particular endemic UPEC strains in the community, as the majority of acute UTIs in a given region are caused by distinct strains of UPEC [4]. These data suggest that in order for the same strain of UPEC continually to cause new infections of the bladder, uropathogenic strains of *E. coli* must be able to maintain themselves in close proximity to the same host following an acute infection. As mentioned above, the GIT and the vaginal/periurethral area are well-documented reservoirs for UPEC [4,5]. The UT has not been considered a reservoir for uropathogenic strains of *E. coli*.

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coli primarily because bacteriuria is cleared following an acute UTI. However, the possibility that UPEC may persist within the bladder mucosa in the absence of bacteriuria has not been excluded, and in fact it has been demonstrated that the bacteriological state of the urine does not necessarily reflect that of the bladder tissue [14]. Recently, it was shown using a mouse model of UTI that UPEC invaded the bladder epithelium and were able to survive for months following the acute infection, despite the fact that the mice were abacteriuric [15]. These findings demonstrate that the UT may be previously unrecognized reservoir for UPEC and suggest that the pathogenesis of recurrent UTIs may be more complicated that originally assumed. This article will focus on the establishment and potential consequences of the bladder reservoir with respect to recurrent infections in the UT.

2. Establishment of a persistent E. coli reservoir in the bladder mucosa

Upon entering the bladder UPEC must adhere to epithelial cells to establish an infection. Type 1 pili are surface adhesive organelles expressed by the majority of UPEC, which are critical for the colonization of the bladder epithelial surface [16]. The current paradigm is that the adherent organisms remain extracellular and are rapidly cleared from the urinary tract by innate host defenses. In contrast to this view, it is now known that UPEC invades bladder epithelial cells; an event mediated by the adhesin of the type 1 pilus, FimH [17,18]. Once inside the lumenal epithelial cells uropathogenic strains of E. coli can replicate intracellularly, forming large bacterial inclusions [15]. However, the attachment to and invasion of bladder epithelial cells triggers numerous host responses including exfoliation and cytokine production [19,20]. The exfoliation response is an effective means of eradicating many of the cell-associated bacteria from the bladder; however, the loss of superficial epithelial cells exposes the underlying bladder epithelium. To survive the exfoliation response and potentially to increase the likelihood of interactions with the underlying epithelium, UPEC are able to re-emerge from infected host cells prior to the completion of epithelial sloughing [15]. In this way, additional bacterial-epithelial contacts are made, potentially with exposed transitional epithelial cells, facilitating the persistence of the organism. Although the bacterial virulence factors involved in the intracellular phase of UTI pathogenesis, besides FimH, are not known, it has been demonstrated that intracellular bacteria have a survival advantage in the urinary tract in vivo [17].

To investigate the potential importance of UPEC persistence in the bladder, the stability of this reservoir was investigated over time. Surprisingly, similar levels of bacteria were recovered at 10 weeks after infection to those present at 3 days after infection in C57BL/6 mice [15]. The majority of the infected mice remained abacteriuric at the time of sacrifice, despite the persistence of bacteria in bladder tissue. Notably, a 3-day course of the antibiotic trimethoprim-sulphamethoxazole (TMP–SMZ) was unable to eradicate persistent bacteria from the bladder, demonstrating that E. coli can persist in the bladder even in the setting of appropriate antibiotic therapy [19]. In summary, UPEC is able to invade into the bladder epithelium during acute UTIs leading to the establishment of a persistent bacterial reservoir. These findings demonstrate that the bladder mucosa represents a previously unrecognized site of chronic bacterial colonization following an acute UTI.

3. Bacterial persistence in the bladder and recurrent bacteriuria

The presence of persistent E. coli in the bladder following an acute UTI suggests that this reservoir could contribute to the pathogenesis of recurrent UTIs. To test this hypothesis mice infected with UPEC were followed by urinanalysis for 6 weeks after infection. Since mice are abacteriuric during the reservoir phase of a UTI, a positive urine culture in a mouse with previously documented sterile urine is indicative of a recurrent bacteriuric episode. Using this analysis it was demonstrated that 36% of mice infected with UPEC will have at least one episode of recurrent bacteriuria with the same bacterial strain during a 6-week observation period (Schilling JD, Lorenz RG, Hultgren SJ, manuscript in preparation). Thus, the mouse model of UTI appears to be a viable experimental system to investigate the mechanisms involved in the pathogenesis of recurrent UTIs.

An intriguing observation made during these mouse studies was that mice infected with UPEC intravesically develop at least transient colonization in the GIT with the inoculated strain of E. coli, in addition to the establishment of a bladder reservoir (Schilling et al., manuscript in preparation). Moreover, even uninfected mice in the same cage as infected mice became colonized in the GIT with the uropathogenic E. coli strain. The association between bacteriuria and inter-mouse spread of UPEC, suggest the possibility of urine–oral spread; however, additional studies will be necessary to confirm this concept. The presence of faecal and bladder reservoirs in the mouse model of UTI further enhances the value of this infection system as a tool to dissect the complexities of recurrent UTIs.

The ability of the UPEC strain to colonize the GIT following intraurethral inoculation of bacteria, suggests that this reservoir may also play a role in the recurrent
bacteriuric episodes observed in C57BL/6 mice. To test whether UPEC from a faecal reservoir could facilitate bladder colonization, persistent GIT colonization was established using an anal lavage method. Despite maintaining high levels of GIT colonization, none of these mice developed UT colonization during the 4-week observation period. Although not definitive, the inability of UPEC in the GIT to efficiently migrate to the bladder argues that the recurrent episodes of bacteriuria that are observed in the mouse model of UTI are a consequence of the bacteria persisting at other sites, of which the bladder is a prime candidate. Additional studies will be necessary to further characterize the specific role of the bladder bacterial reservoir in recurrent infections of the urinary tract.

Although intriguing, the relationship between recurrent bacteriuria in the mouse model and recurrent UTIs in the human population remains to be determined.

However, the similarities between the mouse and human uroepithelium, and the fact that UPEC isolated from humans with acute UTIs readily causes infection in mice suggests that the observations made in the mouse system should be analyzed in humans as well [21]. To this end, bacteria have been identified in the bladder tissue of women with documented recurrent UTIs in the absence of bacteriuria [22]. Thus, the concept of bacteria surviving in the bladder mucosa in the setting of sterile urine has been shown in a human population. Perhaps these findings are also relevant in the significant number of cases where women present with symptomatic UTI, but have no culturable bacteria in their urine (i.e. acute urethral syndrome or interstitial cystitis) [23].

The ability of UPEC to persist within the bladder mucosa following an acute UTI argues that the pathogenesis of recurrent UTIs may be more complicated than previously assumed, and perhaps explains in part, why these infections are so hard to manage in the clinic. It is clear that an initial episode of cystitis is a consequence of uropathogenic bacteria migrating from the GIT to the UT. However, following an acute UTI, bacteria can also persist within bladder tissue. Therefore, the aetiology of subsequent infections becomes more challenging to define as the culprit bacterium could have originated from the GIT again, or re-emerged from a quiescent state within the bladder itself. It seems likely that both mechanisms may be involved in recurrent UTIs. The picture is made more complex by the fact that in the mouse model of UTI bacteriuria is a means of spreading UPEC to the GIT of other hosts within the same local environment. This finding suggests that urine-oral spread may in fact be means to re-establish faecal colonization within the same host and/or to spread to additional hosts. If this is also true in the human population, the relationship between faecal colonization and bladder colonization may be cyclical, making it very hard to eradicate the bacterial strain from affected hosts and from the community at large (Fig. 1). The importance of understanding the mechanisms of UPEC spread between, and persistence within hosts is underscored by the recently documented epidemic of UTIs in the USA [24].

4. Concluding remarks

Recurrent UTIs are common clinical problem. Currently the most effective treatment for these infections is prophylactic antibiotic therapy. However, if the antibiotics are discontinued the UTIs generally return [23]. In order to develop new and better therapies for recurrent UTIs, the pathogenesis of these infections needs to be more completely defined. The current thought is that all recurrences are a consequence of bacteria migrating from the GIT. Although this may account for many cases of recurrent UTIs, several recent findings suggest that the reality is likely to be a more complicated situation involving persistent bacteria in the GIT, the periurethral areas and the bladder. In support of this concept, GIT or periurethral/vaginal colonization alone is not predictive of the risk of a recurrent infection [8,9]. Future work dissecting the interplay between UPEC reservoirs in both the mouse model and with clinically based studies will be necessary for the design of new therapeutic modalities for these troubling infections.
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References


