Novel Mechanism of P-Fimbriated *Escherichia coli* Virulence in Pyelonephritis

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Urinary tract infections (UTI) are among the most frequently encountered community-acquired or nosocomial infections. The disease burden of UTI is estimated to be 150 million cases annually worldwide (1). Catheter-associated UTI is the most frequent source of Gram-negative sepsis in hospitalized patients (2). The spectrum of disease in UTI includes cystitis, pyelonephritis, urosepsis, catheter-related infections, as well as asymptomatic bacteriuria, which requires medical management among certain, more vulnerable hosts. A conservative estimate is that 250,000 cases of pyelonephritis occur annually in the United States, many of which require hospitalization (3). Pregnancy confers an increased risk of pyelonephritis, and UTI is associated with adverse obstetrical and newborn outcomes. Patients with diabetes are also at increased risk of pyelonephritis (4).

*Escherichia coli* is the most common cause of UTI among virtually every patient group and accounts for 80 to 90% of cases of uncomplicated pyelonephritis and cystitis among otherwise healthy women (5). *E. coli* that cause UTI and other uropathogens are distinguished from related members of their genus and species by the presence of specific virulence determinants, microbial adaptations promoting success in the urinary tract (6). Virulence determinants allow uropathogens to overcome intrinsic urinary tract defense mechanisms that normally protect the host against UTI, such as the flow of urine, variable pH and osmolality, lack of nutrients, exfoliation of epithelial cells, and the production of cytokines that result in recruitment of polymorphonuclear leukocytes to the bladder mucosa (6–8). Other clinical factors influence the risk of UTI in a given host, such as acquired and intrinsic differences in host susceptibility, genetic factors, and behavioral exposures. However, numerous epidemiologic, animal, and *in vitro* studies have indicated that virulence determinants of uropathogenic bacteria enhance fitness of these organisms for entering the urinary tract and establishing disease, particularly among otherwise healthy hosts.

The virulence determinants of uropathogenic *E. coli* (UPEC) have been most extensively studied. These include adhesins, such as P, type 1, S, Dr, and FIC fimbriae; toxins and cytolsins, such as cytotoxic necrotizing factor, secreted autotransporter toxin, cytolethal distending toxin, and hemolysin; iron acquisition mechanisms, including aerobactin, enterobactin, and yersiniabactin; and surface components such as capsule, flagellum and lipopolysaccharide (LPS) (6–8). Adhesins are particularly important virulence determinants because the initial event in the pathogenesis of UTI is the adherence of *E. coli* to the urogenital mucosa by infecting *E. coli*, an event mediated by adhesins. Many urovirulence traits, including P fimbriae, are encoded in mobile genetic elements known as pathogenicity islands.

P fimbriae appear to be especially important in *E. coli* pyelonephritis. Epidemiologic studies in adults and children over many years in diverse geographic locations have consistently demonstrated that these adhesins are present in nearly 100% of strains causing pyelonephritis (6,9,10). In a monkey model, P fimbriae are required for the establishment of pyelonephritis and provide a competitive edge for organisms inoculated into the bladder (11,12). In human experiments, P fimbriae enhanced the early establishment of bacteriuria (13).

Each adhesin of UPEC recognizes specific cognate receptor(s) on the surface of the uroepithelium. P-fimbriated organisms bind to a minimal binding site contained in the globoseries glycosphingolipids (GSL) (14–17). Globoseries GSL are especially abundant in the human kidney and their expression is genetically determined, in parallel with the expression of ABH histo-blood group antigens (18–20). Thus, some cognate host receptors for adhesins are associated with tissue specificity and/or intrinsic differences in host susceptibility.

Recent studies of several UPEC adhesins have demonstrated that fimbrial interactions with epithelial cells have further consequences, beyond conferring specificity and functioning as anchors against removal through bulk flow of urine. For example, in a mouse model of UTI, type 1 fimbriae mediate invasion of uroepithelial cells and persistence in the bladder (21). The binding of P fimbriae to uroepithelium results in a ceramide signaling and a mucosal inflammatory response via a Toll-like receptor-4 (TLR4)–dependent pathway (22–25).

In this issue of *JASN*, Rice and colleagues (26) present a carefully designed study showing an entirely new function for P fimbriae: Impairing the local host immune response in a mouse model of pyelonephritis. The polymeric Ig receptor (pIgR) is produced by the renal epithelium and transports IgA into the urinary space.
Secretory IgA (S-IgA) appears to have a key role in protecting the upper urinary tract against infection. S-IgA is significantly elevated in the urine of patients with pyelonephritis, as compared with patients with cystitis or in normal controls (27). In a primate model of UTI, infection with a P-fimbriated E. coli elicited a robust S-IgA response in the urine (28).

Rice et al. infected C3H/HeN (LPS-responsive) mice with either the nonadherent fecal E. coli isolate FN506 transformed with plasmid pBR322 encoding P fimbriae, or with FN506 transformed with the same plasmid, with only P fimbriae sequences deleted. The P-fimbriated organism established pyelonephritis in the mouse and persisted in the kidney to a greater degree than did the identical E. coli strain lacking P fimbriae. Postulating that P fimbriae regulate epithelial pIgR expression and thus IgA transport into the urine, they compared kidney pIgR RNA and protein levels and urine IgA levels in mice infected with the P-fimbriated or non–P-fimbriated organism(s). Infection with the P-fimbriated organism resulted in significantly reduced pIgR RNA and protein levels and a concomitant decrease in urinary IgA levels in mice in contrast to the P-fimbriated organism at the 48-h time point.

Although epithelia are relatively resistant to its effects, LPS of Gram-negative organisms elicits dramatic, broad reaching, and often deleterious effects on many host tissues. Some have argued that bacterial adhesins exist largely to increase the efficiency of LPS delivery. Thus, to distinguish the suppression of secretory IgA pathways from possible LPS-mediated effects, Rice and colleagues conducted parallel experiments in a strain of mice (C3H/HeJ) that is nonresponsive to LPS because of a mutation in TLR-4. In these LPS-insensitive mice infected with the P-fimbriated E. coli, pIgR mRNA and protein levels were likewise decreased. Thus, this negative immunomodulatory effect appears to be independent of the response to E. coli LPS in mice.

In summary, Rice and colleagues have discovered a novel pathoadaptive response of uropathogenic E. coli in mice, in which the organism apparently helps ensure its success in the kidney by suppressing a key local immune defense, secretory IgA. This finding of a host tissue response and subsequent host-bacterial cross talk following bacterial adhesin-mediated binding is, in itself, an advance in the study of bacterial uropathogenesis. However, the finding is particularly key because the resulting suppression of host defenses is a more adaptive outcome for P-fimbriated UPEC than previously described host responses, in which host defense systems are activated through P fimbrial binding.

This study may also explain one of the most consistent and striking findings in the UPEC literature, namely, the nearly universal presence of P fimbriae among isolates from pyelonephritis, in study after study. Although putative E. coli uro-virulence determinants are usually more prevalent among isolates from patients with UTI as compared with isolates from a control group, the distinction is greater in the case of P fimbriae. This finding has long suggested that P fimbriae must be acting through some highly conserved and/or critical function in the host cell, as pathogenic bacteria frequently evolve to co-opt critical host functions, ensuring their own survival. As a corollary, this study suggests that the role of secretory IgA in the defenses of the kidney against infections with Gram-negative organisms is an area for fruitful future investigation.

References

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