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MiniReview

Escherichia coli mediated urinary tract infections: Are there distinct uropathogenic *E. coli* (UPEC) pathotypes?

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Abstract

A variety of virulence genes are associated with *Escherichia coli* mediated urinary tract infections. Particular sets of virulence factors shared by bacterial strains directing them through a particular pathogenesis process are called a "pathotype." Comparison of co-occurrence of potential urinary tract infection (UTI) virulence genes among different *E. coli* isolates from fecal and UTI collections provides evidence for multiple pathotypes of uropathogenic *E. coli*, but current understanding of critical genetic differences defining the pathotypes is limited. Discovery of additional *E. coli* genes involved in uropathogenesis and determination of their distribution and co-occurrences will further define UPEC pathotypes and allow for a more detailed analysis of how these pathotypes might differ in how they cause disease.

Keywords: Urinary tract infections; Uropathogenic *Escherichia coli*; Pathotypes; Virulence factors

1. Introduction

Escherichia coli are a very diverse species of bacteria found naturally in the intestinal tract of all humans and many other animal species. A subset of *E. coli* are capable of causing enteric/diarrhoeal disease, and a different subset cause extra-intestinal disease, including urinary tract infection (UTI). The determination of six different *E. coli* "pathotypes" that cause enteric/diarrhoeal, enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC) and diffusely adherent *E. coli* (DAEC), greatly enhanced our understanding of pathogenic *E. coli*. Each pathotype causes disease using different combinations of virulence factors, with different molecular pathways, and in some but not all cases resulting in disease symptoms that can be distinguished from each other (for review see [1]). This improved understanding of *E. coli* causing enteric/diarrhoeal disease has been very useful relative to therapeutic and vaccine development.

By contrast, pathotypes have yet to be distinguished for UTI, although by analogy, a designation 'uropathogenic *E. coli*' (UPEC) is in common usage. UTIs are one of the most frequently acquired bacterial infections [2] and *E. coli* accounts for as many as 90% of all UTIs seen among ambulatory populations [3]. Overall, approximately half of all women have had a UTI by their late 20s [2]. About 20–30% of women with first UTI will have two or more infections [4]; and, for 5%, chronic recurring infections which greatly disrupt a woman's life

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[5]. In the United States, the annual total direct and indirect costs of UTI in 1995 were estimated to be $1.6 billion as the result of urinary infections suffered by an estimated 11.3 million women [2].

A UTI is defined as a significant number of pathogenic organisms in the urinary system. If symptoms, such as painful or frequent urination or blood in the urine, are present, as few as 100 uropathogenic bacteria per milliliter urine may be considered significant [6]. Bacteria can be detected at high concentrations in the urinary tract in individuals during routine urine examination. However, many of these individuals experience no symptoms. This condition is termed asymptomatic bacteriuria (ABU). Cases of symptomatic bacteriuria are classified either as cystitis (CY) when infection is limited to bladder or pyelonephritis (PY) when the kidney is infected [7]. While cystitis in the otherwise healthy individual generally resolves without sequelae, pyelonephritis can cause serious morbidity and can be fatal. Patients with abnormal or obstructed urinary tracts or with compromised immune systems are at high risk of UTI. These infections are often referred as complicated UTIs. There is an increased risk in this group that a simple urinary tract infection may progress to systemic infection.

Unlike enteric/diarrhoeal diseases that often occur in clear epidemiologic clusters, UTI epidemics are, as yet, difficult to identify. The high background rate of UTI [2], the impression that UTI among ambulatory patients is caused solely by auto-infection, and the great diversity of *E. coli* obscures potential epidemics. To the best of our knowledge, only one UTI outbreak has been reported among ambulatory patients. In Greater Copenhagen, Olesen et al. identified a cluster of multi-resistant, lactose-negative *Escherichia coli* O78:H10 causing urinary symptoms among 14 community members. Only the unusual lactose-negative phenotype made the cluster visible [8]. This lack of epidemiologic clusters has made it much more difficult to determine if there are separate pathotypes of UPEC.

Several recent reviews give detailed overviews of UPEC pathogenesis factors [1,9–12]. Here, we present a brief summary of what is currently known about UPEC virulence genes, and then examine the evidence for the existence of distinct UPEC pathotypes with different sets of virulence genes that help determine the specific *E. coli*–host interactions that lead to urinary tract infections.

2. Summary of currently studied UPEC virulence genes

Table 1 presents a set of *E. coli* genes that have been potentially implicated as important in allowing some UPEC isolates to establish urinary tract infections. The first one we will discuss is the *fim* gene cluster that encodes the proteins responsible for type 1 pilus production. Unlike the other genes in Table 1, the *fim* genes are not present in a statistically significantly higher set of UPEC vs. rectal isolates as almost all *E. coli* have the *fim* genes. However, as is true with many of the pilus gene clusters in *E. coli*, type 1 pilus expression is regulated in part by a phase-variation system. Gunther IV et al. [19] compared the fate of mutants phase-locked in either the on or off configuration in a mouse model of ascending urinary tract infection and found that the locked-off mutants were recovered from the urine, bladder and kidneys 24 h post-inoculation in significantly

Table 1
Putative uropathogenic *E. coli* (UPEC) virulence factors and proposed function or homology

Genes (virulence factor)	Function or homology	Reference[a]
cnf1 (cytotoxic necrotizing factor 1)	Causes multinucleation and rounding of human cells	[13–15]
cvaC (colicin V)	Colicin	[16]
drb (Dr family of adhesins)	Adherence factors that bind decay acceleration factor (DAF)	[13,17,18]
fim (type 1 pili)	Adherence to uroepithelial cells and FimH mediated invasion	[19–21]
hly (α-hemolysin)	Lyses red blood cells	[13,22,23]
hra (heat-resistant agglutinin)	Adherence factor	[24]
iha (IrgA homolog adhesin)	Adherence factor	[25–27]
$iroN_{E.\ coli}$ ($IroN_{E.\ coli}$)	Siderophore receptor	[25,27,28]
iucD (aerobactin)	Siderophore that binds iron	[13,29]
kpsMT (group II capsule)	Capsular polysaccharide production	[13,25]
ompT (OmpT)	Outer membrane protease	[13,25]
$papG_{AD/IA2}$ (class II P-pili)	Adherence to uroepithelial cells	[10,13,30]
$prsG_{J96}$ (class III P-pili)	Adherence to uroepithelial cells	[10,13,30]
picU (PicU)	Homolog to Pic (protein involved in intestinal colonization) serine protease autotransporter	[31,32]
sat (Sat)	Serine protease autotransporter toxin	[33,34]
sfa (S-fimbrial family)	Adherence factors	[13,35]
usp (uropathogen specific protein)	Bacteriocin	[25,27,36]
vat (Vat)	Vacuolating autotransporter toxin	[37,38]
$PaiII_{cft073}$	Multiple genes	[39,40]

[a] Due to space limitations, only up to three references purporting UTI virulence association for each gene are listed.