Chapter

Virulence Factors of Uropathogenic *Escherichia coli*

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Abstract

Uropathogenic *Escherichia coli* (UPEC) strains are those that cause infections in the urinary tract. They acquired virulence factors which enable them to survive in the urinary tract and elicit pathogenicity. The virulence factors are classified into two categories: (i) bacterial cell surface virulence factors and (ii) bacteria secreted virulence factors. Adhesins, toxins and iron up-take systems are major groups of virulence factors. The variety of virulence factors of UPEC is presented in this chapter.

Keywords: extraintestinal *E. coli*, uropathogenic *Escherichia coli*, urinary tract infection

1. Introduction

Uropathogenic *Escherichia coli* (UPEC) is a type of extraintestinal pathogenic *E. coli* (ExPEC) responsible for urinary tract infection (UTI). It is reported to be the ExPEC with the greatest medical importance. This is so because UPEC is responsible for most of the UTIs and humans of all ages are affected [1, 2]. These bacteria are associated with both asymptomatic bacteriuria and symptomatic UTIs. UTIs are categorized based on the parts of the body which the infections occur. These are cystitis which occurs in the bladder and pyelonephritis which occurs in the kidney [3–6]. UPEC strains have a lot of virulence factors which are responsible for the pathogenicity associated with symptomatic UTIs [7, 8]. The virulence factors are classified into two categories: (i) bacterial cell surface virulence factors and (ii) bacteria secreted virulence factors [9–11]. Many of virulence-associated genes can be found on pathogenicity islands (PAIs) [12, 13]. Though the mechanisms of asymptomatic bacteriuria are still not clear, studies have reported that UPEC becomes nonadherent and nonhemolytic resulting to asymptomatic bacteriuria [14–16]. Thus, this chapter will elucidate on the important UPEC virulence factors which are responsible for UTIs.

2. Adhesins of uropathogenic *Escherichia coli*

Adhesins are adhesive organelles, notably fimbriae, that promote bacterial colonization. Some adhesins also promote bacterial invasion of the host cell. Adhesins are thought to be the most important virulence-associated molecules which function in UPEC pathogenicity. The adhesins can also directly trigger host and bacterial cell signaling pathways. They can also facilitate the delivery of other

bacterial products to the host tissues [17]. Prominent bacterial cell surface virulence factors, which play significant roles in UPEC pathogenicity include type 1 fimbriae [11]; Class I, Class II, and Class III of P-fimbriae [18–20]; Dr. family of adhesins for binding to the decay-accelerating factor (DAF) [21]; Curli fimbriae which functions as binding factor and biofilm producer [22]; and S-fimbriae [14, 23, 24]. Type 1 fimbriae have the most significant effects in UTIs as they enhance bacterial survival and growth, enhance inflammatory reaction at the mucosa, bacterial invasion, and control biofilm production [7]. P-fimbriae have the second most prominent role in UPEC-associated pathogenesis of human ascending UTIs and pyelonephritis. They promote UPEC adherence to the matrix of the mucosa and tissues and trigger cytokine production [25–30].

3. Toxins of uropathogenic *Escherichia coli*

UPEC secrete several virulence toxins which are responsible for the damage of the host cells and host inflammatory response. α-hemolysin (HlyA) is the most virulent toxin produced by UPEC. The effects of HlyA in UTIs are dependent on its dosage produced by UPEC. At high concentration, HlyA destroys the erythrocytes and allow UPEC to break through the mucosal barriers, damage immune system, and depletes iron stores of the host [31–34]. At low concentration, HlyA induces cell death in the bladder using proinflammatorycaspase-1/caspase-4. This causes kidney damage and scarring; oscillations of Ca2+; ascension and colonization of ureters and kidney parenchyma in the renal tubule epithelia resulting in the disruption of normal flow of urine [35–38]. The stimulation of *in vitro* production of actin stress fibers and membrane ruffle in a Rho GTPase-dependent manner is enhanced by cytotoxic necrotizing factor 1 (CNF1) produced by many strains of UPEC. This also facilitates the invasion of UPEC into the kidney cells [39, 40]. However, the extensiveness of CNF1 activities in causing invasion-associated pyelonephritis is not well understood and it has different schools of thoughts [41]. CNF1 also causes polymorphonuclear phagocytosis to trigger apoptosis and scarring of the epithelia of the bladder [42]. The uropathogenic specific protein (Usp) is important in the movement of UPEC from the urinary tract to the bloodstream. High prevalence of Usp has been reported UPEC isolated in cystitis, pyelonephritis, and prostatitis [43]. Serine-autotransporter toxin (Sat) secreted by UPEC is toxic to the cell lines of bladder or kidney origin thereby enhancing pathogenesis of UTI [44, 45]. Also, cytolethal distending toxin (CDT) is another toxin secreted by UPEC which is virulent in UTIs [46, 47].

4. Iron uptake systems of uropathogenic *Escherichia coli*

Urinary tract has limited iron. However, UPEC are able to produce small iron chelator molecules, known as siderophores, to scavenge ferric iron (Fe3+) in the host. The most prominent ones are yersiniabactin, salmochelin, and aerobactin [48, 49]. The yersiniabactin and its receptor, FyuA, are encoded in a PAI [50, 51]. It has also been reported that for efficient biofilm formation by UPEC, FyuA is required [52]. UPEC also secretes another important hydroxamate siderophore called aerobactin. This is produced from the condensation of two lysine and a citrate molecules. During UPEC invasion, the bacterium secretes salmochelin. Its outer membrane siderophore receptor (IroN) transports different catechol siderophores, including N-(2,3-dihydroxybenzoy)-L-serine and enterochelin also called enterobactin [53]. Enterobactin has less solubility and stability than

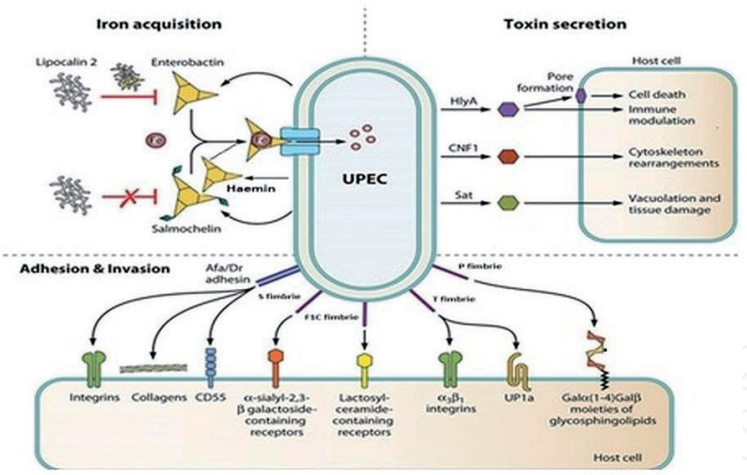

Figure 1.
UPEC-associated fitness and virulence. Adapted from the work by Servin [64].

aerobactin [54–56] but has higher iron affinity than aerobactin in aqueous [55, 57]. UPEC also uses enterobactin for Fe3+ scavenging in the urinary tract [9]. However, enterobactin can be inactivated by the host proteins such as serum albumin and siderocalin thereby preventing its uptake [58]. UPEC overcomes this instability by modifying the enterobactin to salmochelin by glucosylation through the enzymatic action of glucosyltransferase and prevents it from being recognized by the host proteins [9]. Also, UPEC has another iron acquisition system called haemin uptake system consisting of Ton-B dependent receptor (ChuA) and heavy metal associated (*Hma*) receptor that takes part in direct upregulation of haem receptors from free iron during UPEC infection. This system has also been reported to play significant role in the formation of biofilm [59–61]. The expression of ChuA is controlled by other regulatory proteins. It has been reported that the production of ChuA is triggered as RfaH increases [62]. However, Hma does not depend on ChuA and it is controlled by Tyr-126. Both Hma and ChuA are associated with haem uptake for optimal kidney utilization [63]. **Figure 1** shows the diagram of UPEC-associated fitness and virulence factors.

5. Lipopolysaccarides of uropathogenic *Escherichia coli*

Lipopolysaccharide (LPS) is a major part of the cell wall which has highly conserved lipid A-core and repeating O-antigen subunits which vary in different strains of *E. coli* depending on the sugar residues and their linkage patterns within the repeating subunits [41, 65]. LPS is very prominent in activating the host immune response and the stimulation of nitric oxide and cytokine (IL-1, TNF-α) for inflammatory response [11, 66]. Also, it triggers the production of specific antibodies to the somatic antigen and the humoral immune response to other antigens of the pathogen [31]. Several antigenic types of LPS help UPEC to escape being killed by the host serum [31]. A study on animal models has reported that LPS-associated acute renal failure is due to the response of the host to the LPS and not based on the expression of TLR4 (LPS receptor) in the kidney [66].

6. Capsule of uropathogenic *Escherichia coli*

Capsule is made up of polysaccharides and it covers and protects UPEC from various harsh environmental conditions [66]. The capsule helps UPEC to resist

phagocytosis and bactericidal effects of complements in the host. It also confers antimicrobial resistance and antiserum activity to UPEC [54, 61]. Capsules like K1 and K5 interfere with the proper response of the humoral immunity of the infected host [66]. The K1 polysaccharide plays a significant role in intracellular bacterial community (IBC) development and the pathogenesis of several UTI stages [54, 67].

7. Other virulence factors of uropathogenic *Escherichia coli*

Toll receptor (TIR)/interleukin1 (IL-1) receptor domain-containing protein (TcpC) is a novel class of virulence factors that destabilize TIR signaling for UPEC to survive during UTIs [68]. Interaction of TcpC with myeloid differentiation primary response 88 (MyD88) found in the host ends the downstream signaling pathways mediated by TLRs [69].

UPEC produces outer membrane protease T (OmpT) that catalyzes plasminogen activation to plasmin [70]. OmpT helps UPEC to persist in the urinary tract when protamine and other cation peptides cleave with antibiotic activity [71, 72]. UPEC also decreases cytokines production by blocking nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [68]. In **Table 1**, prominent UPEC virulence factors, their role and genetic markers are presented.

Virulence factor	Role	Genetic markers/gene name	References
Afimbrial adhesions	Binding factor	*afa*	[23, 24, 54]
Cytotoxic necrotizing factor 1	Toxin	*cnf1*	[38, 39]
Curlifimbriae	Binding factor	*csgA-G*	[22]
Dr family of adhesions	Binding factor	*drb*	[21]
Haemin	Iron uptake and biofilm formation	*hmn*, *chuA*	[59–61]
Type 1 fimbriae	Binding factor	*fimH*	[8]
Ferric yersiniabactin uptake receptor	Iron uptake and biofilm formation	*fyuA*	[62]
α-hemolysin	Lyses red blood cells	*hlyA*	[33]
Salmochelin	Siderophore receptor	$iroN_{\text{E. coli}}$	[51]
Aerobactin	Iron chelation and uptake	*iucD, iutA*	[50]
Outer membrane protease T	Outer membrane protease production to degrade protamine peptides	*ompT*	[73, 74]
Uropathogen specific protein	Movement of UPEC from the urinary tract to the bloodstream	*usp*	[42]
Class I, Class II, and Class III P-fimbriae	For binding to the uroepithelial cells	*papGJ96, papGAD/IA2, and prsGJ96*	[18, 20, 21]
Serine-protease autotransporter toxin	Vacuolation and tissue damage	*sat*	[73, 74]
S-fimbrial family	Binding factor	*sfa*	[8, 23, 24]

Table 1.
Virulence factors of uropathogenic Escherichia coli *and their functions.*

8. Conclusion

Apart from possessing virulence factors, for the medical importance of *E. coli* strains the ability to form biofilms is also significant. Biofilms play a major role in urology. Biofilms are namely usually associated with pyelonephritis and chronic or recurrent infections [75]. Biofilm formation is a complex process that may involve multiples adhesins and factors [76]. Biofilm contributes to bacterial resistance [60, 77–81]. Studies have reported that biofilm production mediated by co-expression of curli and cellulose facilitates in *E. coli* helps UPEC to survive in the urinary tract for a long time through the production of an inert, hydrophobic extracellular matrix which surrounds the organism [60, 77, 78].

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