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Biofilm Formation in Uropathogenic *Escherichia coli* Strains: Relationship with Urovirulence Factors and Antimicrobial Resistance

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1. Introduction

1.1 *Escherichia coli* virulence and urinary tract infections

Urinary tract infections are a major public health concern in developed countries and also represent one of the most common hospital-acquired infections. Most uncomplicated UTIs are caused by *E. coli*, accounting for up to 90% of community-acquired and approximately 50% of nosocomial UTIs (Vila et al., 2002). The origin of these strains is frequently the patient's own intestinal flora. In comparison to commensal strains, UPEC present several virulence factors that allow them to colonize host mucosal uro-epithelium, injure and invade host tissues, overcome host defence mechanisms, incite a host inflammatory response and eventually proceed from the lower urinary tract to the renal cavities and tissues. The virulence factors involved in UTIs include surface virulence factors such as type 1 fimbriae, P, S and F1C fimbriae; exported virulence factors such as α-haemolysin, cytotoxic necrotising factor 1 (CNF1), secreted autotransporter toxin (SAT), cytolethal distending toxin (CDT) and cytolysin A (Caprioli et al., 1987; Lai et al., 2000; Smith et al., 1963; Tóth et al., 2000).

A common problem in UTI is recurrence, even in patients without anatomic abnormalities or indwelling bladder catheters. It is estimated that 40 to 50% of adult healthy women have experienced at least one UTI in their lifetime, and there is a tendency for these infections to become chronic due to a high rate of recurrence (Ulett et al., 2007). The persistence of the same *E. coli* strain in the urinary tract may be the cause of recurrent prostatitis. In fact, it has been shown that after an episode of acute prostatitis, cultures of expressed prostatic secretions are still positive three months after the end of a six-week course of therapy in one third of men (Kravchick et al., 2004). This may be related to the capacity of bacteria to form biofilm structures. Biofilm can promote persistence in the urinary tract and on biomaterial surfaces by protecting bacteria from the clearing out effect of hydrodynamic forces and the killing activity of host defence mechanisms and antibiotics (Hanna et al., 2003).

1.2 Biofilm and factors involved in its formation

Biofilm is defined as a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface (Costerton et al., 1999). Biofilm formation is carried out in four steps: adhesion or attachment, early development of biofilm structure, maturation and dispersion of cells from the biofilm into the surrounding environment and return to the planktonic state.

Several surface determinants are involved in biofilm formation such as:

1.2.1 Flagella and motility

Motile *E. coli* generally present multiple peritrichous flagella. Motility is involved in colonization of host organisms or target organs and promotes initial cell-to-surface contact.

1.2.2 Fimbriae

Fimbriae are one of the virulent factors associated with host tissue adhesion of pathogenic *E. coli* strains (Finlay et al., 1997). Among these, type 1 fimbriae are the most common among *E. coli* and have an important role in the initial attachment to abiotic surface in biofilm formation (Pratt et al., 1998).

1.2.3 Autotransporter proteins

These secretory proteins present all the requirements for secretion across the cytoplasmic and the outer membrane to the bacterial cell surface (Desvaux et al., 2004). Among these proteins Ag43, AIDA (adhesin involved in diffuse adherence) and TibA are involved in adhesion. Antigen 43 promotes aggregation of cells through Ag43-Ag43 interactions by an intercellular handshake mechanism (Hasman et al., 1999). Ag43 and type 1 fimbriae are expressed co-ordinately in the cells which normally produce only one type of adherence structure at a time (Schembri et al., 2001). AIDA and TibA are autotransporters with homology to Ag43.

1.2.4 Curli

Curli fimbriae aggregate at the cell surface to form 6- to 12-nm-diameter structures whose length varies between 0.5 and 1 μm. Curli adhesive fibres also promote biofilm formation to abiotic surfaces both by facilitating initial cell–surface interactions and subsequent cell–cell interactions (Cookson et al., 2002; Uhlich et al., 2006; Vidal et al., 1998).

1.2.5 F conjugative pilus

The F-pilus promotes both initial adhesion and biofilm maturation through nonspecific attachment to abiotic surfaces and subsequent cell-to-cell contacts which stabilize the structure of the biofilm (Ghigo et al., 2001; Molin & Tolker-Nielsen, 2003; Reisner et al., 2003).

1.2.6 Exopolysaccharide production

The biofilm matrix is composed by exopolysaccharide. This matrix forms a hydrated viscous layer which protects embedded bacteria from desiccation and from host defences because bacteria forming this structure may not be recognised by the immune system. The matrix

may also be involved in the protection of the bacteria against toxic molecules such as antimicrobials, hydroxyl radicals, and superoxide anions). The biofilm matrix could also inhibit wash-out of enzymes, nutrients, or even signalling molecules that could then accumulate locally and create more favourable microenvironments within the biofilm (Redfield et al., 2002; Starkey et al., 2004; Welch et al., 2002). All these aspects of the matrix could contribute to development of phenotypic resistance of pathogenic *E. coli* biofilms and lead to persistent infections (Anderson et al. 2003; Justice et al. 2004). In addition, the exopolysaccharide interactions with other components of the matrix favour the three-dimensional growth of the biofilm (White et al., 2003). The exopolysaccharides most frequently found in the matrix are poly-β-1,6-N-acetyl-glucosamine, cellulose, colanic acid, lipopolysaccharides and capsules.

In this chapter, the role of biofilm in urinary tract infections and its relation with virulence factors and antimicrobial resistance is explained.

2. Evolution of antimicrobial resistance in uropathogenic *Escherichia coli* (UPEC)

Several studies have demonstrated an increase in antibiotic resistance levels in *E. coli* causing community-acquired urinary tract infection (UTI) (Barret et al., 1999; Daza et al., 2001; Goettsch et al., 2000; Goldstein, 2000; Gupta et al., 2001a). Some authors have suggested that most of these studies are likely to reflect a selection bias because few UTIs are being cultured routinely and culture results are available from patients with complications, recent treatment, and recurrence of infection or suspected resistance (Gupta et al., 2001b). However, taking into account the worldwide increase in antibiotic resistance, this factor can be a major problem in complicated and uncomplicated community-acquired UTIs. Hence, as suggested by the Infectious Diseases Society of America (IDSA), knowledge of local resistance rates and surveillance studies to monitor changes in the susceptibility of *E. coli* is highly recommended. (Warren et al., 1999)

Cotrimoxazole has been the drug of choice for empiric therapy of uncomplicated UTI in women during several years. However, resistance to this compound is higher than 20% in many countries. In Spain, a multicentre study performed in 2006 found a resistance level of 32%, (Andreu et al., 2008) quite similar to the result of 33.9 %found in a previous study completed four years beforehand (Andreu et al., 2005), making the differences found between regions noteworthy (range 23% to 37.3%). Results from a single centre also in Spain found a resistance rate of 25%, with isolates from complicated UTIs (28%) being more resistant than those than from uncomplicated UTIs (22%) (Alós et al., 2005). In the USA, resistance to cotrimoxazole has risen from 15% in 1998 to 21.3% in 2003-2004 (Gupta et al., 2001b)). Again, geographic variations were observed in another study among states (15% to 40%) in the USA and in Canada (10.2 to 48.5%) (Zhanel et al., 2006).

Betalactam antibiotics are widely used in the treatment of UTIs. Among them, ampicillin or amoxicillin are not recommended as first line drugs due to high levels of resistance. In the multicentre study from Spain (Andreu et al., 2008) the rate of resistance was 60.7% with clear differences between regions, the lowest value being 36.8%. Despite ampicillin not having been used to treat uncomplicated cystitis for a long time, resistance to this compound has increased along the years. Amoxicillin plus clavulanic acid shows a high

level of activity compared to ampicillin. Resistance to this drug was only found in 8.1% of isolates with a variation according to geographic zones of 3% to 18.3% (Andreu et al., 2008). Other oral betalactams like cefuroxime (8.9% of resistance) or cefixime (6.9% of resistance) show good activity against *E. coli* urinary isolates, but resistance to both drugs was higher in elderly patients (>60 years)(Andreu et al., 2008). An *E. coli* producer of extended spectrum betalactamases should always be considered as an aetiological agent of UTIs. In the Spanish multicentre study (Andreu et al., 2008) this agent represented 5.2% of *E. coli* isolates with most (79.1%) being recovered from patients over the age of 60 years. These isolates are also frequently resistant to fluorquinolones and cotrimoxazole.

Fluorquinolones can be an option to treat UTIs, but their utility is hampered by resistance rates. In Europe, resistance to ciprofloxacin in UPEC was low in the period from 1999-2000, with the highest values found in Portugal (5.8%) and Spain (14.7%) (Kahlmeter, 2003). The multicentre study published by Zhanel et al. (2006) reported a rate resistance in UPEC of only 1.1% in Canada and 6.8% in the USA, with great differences between regions (2.9% to 20.3%). In the Spanish multicentre study (Andreu et al., 2008) resistance to ciprofloxacin was found in 23.9% of all UPEC isolates and, again, significant geographical differences were found (12.5% to 37.3%). Interestingly, the study by Alós et al., (2005) showed that resistance to ciprofloxacin was higher in UPEC recovered in complicated UTIs (19.5%) than in UPEC isolated in uncomplicated UTIs (8.5%). Both studies found that elderly patients showed higher levels of resistance to fluorquinolones.

Nitrofurantoin shows a good activity against UPEC isolates with only 3.8% resistant isolates (Andreu et al., 2008). However, dosage and potential pulmonary toxicity limits their usefulness. Fosfomycin remains as the most active oral antibiotic against UPEC isolates. Resistance to this drug was of 1.7% in the multicentre study published by Andreu et al., (2008) and the compound usually maintains its activity against ESBL producers.

3. Relationship between virulence factors and antimicrobial resistance in UPEC

The level of quinolone-resistance in *E. coli* clinical isolates has steadily increased in most European countries. When the analysis is stratified according to the different UTIs it is found that the percentage of quinolone-resistant *E. coli* isolates causing pyelonephritis is lower that those causing cystitis (Velasco et al., 2001). This data suggested that the quinolone-resistant *E. coli* lost the ability to colonize the kidney epithelia. In order, to prove this hypothesis a study investigating some urovirulence factors in nalidixic acid resistant *E. coli* clinical isolates compared with a group of quinolone-susceptible clinical isolates was carried out. Haemolysin, cytotoxic necrotizing factor-1 (CNF-1) and the autotransporter toxin (sat) were less prevalent in nalidixic acid-resistant than in nalidixic acid susceptible strains. These results suggested that resistance to quinolones may be associated with a decrease in the presence of some virulence factors in uropathogenic *E. coli* (Vila et al., 2002). A study related quinolone resistance and low virulence with phylogenetic origin, mainly in phylogenetic group A, which show a high level of resistance to quinolones and has a low number of urovirulence factors (Johnson JR, et al., 2003). Among the four phylogenetic groups (A, B1, B2 and D), B2 is considered the most virulent. Therefore in a subsequent study, 31 virulence factors were analyzed among nalidixic acid-susceptible and –resistant *E.*

coli clinical isolates from phylogenetic group B2 and again haemolysin and CNF-1 were less prevalent among nalidixic acid-resistant *E. coli* strains (Horcajada JP, et al. 2005). All three genes (*hly*, encoding haemolysin; *cnf*, encoding the cytotoxic necrotizing factor and *sat*, encoding the autotransporter toxin) have their localization in pathogenicity islands in common. Therefore, we thought that the link between the acquisition of resistance to quinolone and lower prevalence of some virulence factors could be explained by the fact that quinolones have been shown to induce the SOS system (Phillips I. et al., 1987) and this induction can favour the release of a genome phage integrated in the bacterial chromosome. Since the structure of the genome phage and the pathogenicity islands is genetically similar it can be hypothesized that the induction of the SOS system by quinolones would favour the release and loss of the pathogenicity island. Indeed, this hypothesis was proven incubating haemolysin-positive, quinolone-susceptible *E. coli* strains with subinhibitory concentrations of ciprofloxacin and searching for haemolysin-negative *E. coli* mutants. It was shown that these mutants can suffer a partial or total loss of the pathogenicity island, carrying the *hly* and *cnf* genes through a dependent and independent SOS pathway, respectively (Soto et al., 2006). All the abovementioned results suggest that the acquisition of quinolone resistance may generate *E. coli* strains with lower virulence.

4. Relationship between biofilm formation, urovirulence factors and antimicrobial resistance

Biofilm formation may be considered as another pathogenic determinant which allows the strains to persist a long time in the genito-urinary tract and interfere with bacterial eradication. Biofilm endows bacteria with several advantages, such as the acquisition of antibiotic tolerance, expression of several virulence factors and an increased resistance against phagocytosis and other host defence mechanisms. Actually, biofilms are probably the usual living condition of bacteria in natural environments and they are, indeed, regularly involved in infections associated with biomaterials such as catheters or prostheses. In these clinical processes, biofilm formation is the main culprit of the characteristic persistence of the infection, despite appropriate antibiotic therapy and hydrodynamic forces (Hanna et al., 2003). More than 50% of all bacteria infections reported involve biofilm formation (Costerton et al., 1999).

Acute UTI caused by UPEC can lead to recurrent infection, which is denominated "relapse" when it is caused by the same strain as that involved in the original UTI or as "re-infection" when it involves different strains. Approximately 25% of women with an episode of acute cystitis later develop recurrent UTI being an important burden to the health system. A study of women with recurrent UTI showed that 74% of strains causing relapse were biofilm formers (Soto et al., 2007). It had been demonstrated that uropathogens can persist within the bladder tissue in underlying epithelial cells or creating pod-like bulges on the bladder surface being a source of recurrent UTI (Mulvey et al., 2000; Anderson et al., 2003). Two virulence factors related to iron-uptake system, yersiniabactin and aerobactin, have also been associated with relapse (Johnson et al., 2001; Soto et al., 2006) due to the need of the bacteria to capture iron for growth in a stressful environment such as the vagina. However, biofilm production may be the key determinant for the persistence of UPEC in the vaginal reservoir, the bladder epithelial cells or both.

The study of the factors contributing to biofilm formation may be important to conceive new therapeutic solutions for the treatment of these infections. On comparing UPEC collected from patients with cystitis, pyelonephritis or prostatitis it had been observed that strains causing prostatitis presented a higher capacity to form "in vitro" biofilm than those causing cystitis and pyelonephritis (Soto et al., 2007). The increased capacity to form biofilm of these strains could be a possible explanation for the persistence of such strains in the prostatic secretory system.

Wu and colleagues (Wu et al., 1996) suggested that the inhibition of bacterial attachment to an uroepithelial surface, a crucial initial event involving precise interactions between groups of bacterial adhesive molecules called adhesins and their cognate urinary tract receptors, could be interesting to avoid biofilm formation. One of the virulence factors involved in the initial steps of biofilm is type 1 fimbriae which play an important role in the adhesion to the host epithelial cells (Prüss et al., 2006) and confer binding to α-D-mannosylated proteins, such as uroplakins, which are abundant in the bladder (Wu et al., 1996). It had been found that biofilm-producing *E. coli* strains showed a significantly greater type 1 fimbriae expression than non-biofilm producing strains (Soto et al., 2007).

Another mechanism by which UPEC promotes the formation of biofilms is via expression of proteins that mediate cell-cell aggregation (Ulett et al., 2007). Of these, Ag43 is also associated with the early stages of biofilm development (Schembri et al., 2003), although it has been demonstrated that the Ag43 can be dispensable for biofilm formation being replaced by alternative factors, such as conjugative pili (Guigo et al., 2001; Reisner et al., 2003). Ag43 is expressed on the surface of UPEC cells located within intracellular biofilm-like bacterial pods in the bladder epithelium, indicating that it may contribute to survival and persistence during prolonged infection (Anderson et al., 2003).

On the other hand, among of the virulence factors studied, only haemolysin seems to present an association with biofilm production. In fact, haemolysin-positive UPEC strains were strongly linked to prostatitis also shown to have a higher frequency of "in vitro" biofilm formation (Andreu et al., 1997; Johnson et al., 2005; Mitsumori et al., 1999; Ruiz et al., 2002; Soto et al., 2007; Terai et al., 1997). These data confirm that the tropism and invasiveness of *E. coli* strains for the prostate rely mainly on haemolysin but also provide a possible explanation for the persistence of such strains in the prostatic secretory system by means of their increased ability to form biofilm.

It has been previously reported that most *E. coli* isolates collected from faeces belong to phylogenetic groups A and B1, with phylogenetic groups B2 and D being the most frequently isolated in urine and considered as virulent. The differences in the phylogenetic background of these two groups of isolates from urine and faeces indicate that the prostate was not, in most of the cases, colonized by commensal bacteria from the intestinal tract. Strains belonging to phylogenetic group B2 presented a higher capacity to form biofilm than those belonging to phylogenetic groups A, B1 and D (Soto et al., 2007).

A relationship between nalidixic acid susceptibility and "in vitro" biofilm formation seems to exist. Studies comparing biofilm positive UPEC strains versus biofilm negative UPEC strains showed that the percentage of nalidixic acid resistant strains was higher among those non-biofilm formers than among biofilm-formers (Soto et al., 2007). In fact, acquisition of quinolone resistance causes a decrease in the "in vitro" production of biofilm by a decrease

in the expression of type 1 fimbriae, avoiding the first step of biofilm formation, the adhesion to the surfaces (unpublished data).

5. Conclusion

Biofilm formation is an important feature related to relapsed UTI, and likely plays an important role in prostatitis caused by *E. coli.* In addition, a link between acquisition of quinolone resistance acquisition and decrease in biofilm formation and loss of some virulence factors has been suggested.

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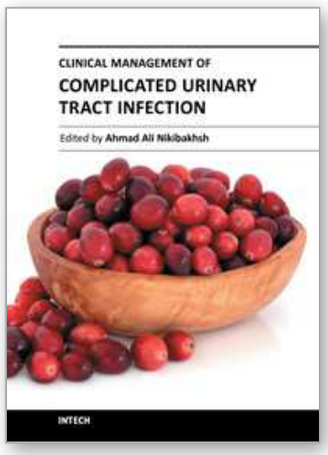

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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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