Virulence Factors Of Uropathogenic *Proteus Mirabilis* - A Mini Review

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Abstract: Proteus mirabilis is a common causative agent of the urinary tract. This microorganism expresses several virulence factors. In uropathogenesis processes P. mirabilis can expresses adhesins, flagella, toxins, enzymes, quorum sensing and immune evasion factors. This review describes some aspects of virulence factors of uropathogenic P. mirabilis.

Index Terms: Proteus mirabilis, virulence factors, uropathogenesis.

1 Introduction

The urinary tract is formed by kidneys, ureters, bladder, and urethra. The urinary tract infection (UTI) is defined as infection or colonization of the urinary tract (urethra, bladder, ureter and kidney) by microorganisms, being the most common bacterial infections. The most common bacterial uropathogens in UTI are: Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis and Enterobacter cloacae [1]. P. mirabilis is a common cause of UTI in the complicated urinary tract, most frequently in patients with indwelling catheters or structural abnormalities of the urinary tract [2]. P. mirabilis expresses several virulence factor involved in uropathogenesis like adhesins, flagella, toxins, quorum-sensing, enzymes and immune invasion [3]. This mini review focus on P. mirabilis pathogenicity factors in the context of uropathogenesis.

2 Adhesins

Bacterial adhesion to the uroepithelium is an essential step for colonization and infection, particularly in a system of continuous urinary flow. Analysis of the genome sequence of P. mirabilis demonstrated a total of 17 potential fimbrial adhesins [4]. At the moment, only 5 fimbriae have been studied: mannose-resistant/Proteus-like (MR/P) fimbriae, P. mirabilis fimbriae (PMF), uroepithelial cell adhesion (UCA) (NAF), ambient-temperature fimbriae (ATF), and P. mirabilis P-like pili (PMP) [5].

2.1 MR/P fimbriae

The MR/P fimbriae are the best understood and most important fimbriae of P. mirabilis. This fimbria is assembled through the chaperone–usher pathway [6]. The MR/P gene cluster is constituted by two transcripts mrpABCDEFGHJ (mrp operon) and mrpI [6]. Several studies have been demonstrated association of MR/P fimbriae and uropathogenesis in murine model. Other studies have been demonstrated that this fimbria is immunogenic and can be used as vaccination target [5].

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2.2 UCA/NAF

The UCA/NAF is organized as long and flexible rods. The role of these fimbriae in the virulence of P. mirabilis was determined by two studies. Cook et al., 1995 showed the adhesion to the uroepithelial cells in vitro model. Pelegrino et al [7], demonstrated that UCA/NAF plays an important role in the colonization of the urinary tract using a UCA mutant and wild-type strains in murine model of infection. The uca operon contains five genes denominated PMI0532-PMI0536 of the genome sequence of HI4320 [4].

2.3 ATF

The ATF fimbriae are important in ambient P. mirabilis life style. This fimbria optimal expression is only in 23°C [8]. Zunino et al., [9] shown no significant difference of ATF mutant strain and wild-type in a murine model of urinary infection. Taken together these fimbriae are not important in P. mirabilis host colonization.

2.4 PMF

The PMF fimbriae were characterized by Massad and Mobley [10]. The genetic organization of the PMF fimbriae operon revealed five functional genes pmfACDEF [10] , [4]. Zunino and co-workers [11] determined the role of PMF in the virulence of P. mirabilis. This study suggests an important role of this fimbria in P. mirabilis colonization of bladder and kidneys.

2.5 PMP

The PMP fimbriae were isolated and identified by Gaastra et al. [12]. These fimbriae were characterized from P. mirabilis strain isolated from a dog with urinary infection. PMP are present in the genome of human P. mirabilis uropathogenic strain HI4320. The genetic operon organization contains 9 genes (PMI2216-PMI2224) [4]. More studies need to be carried out to confirm the participation of PMP fimbriae in the pathogenesis of P. mirabilis.

3. Motility

P. mirabilis initiates the colonization of the urinary tract colonizing the periurethral region. Then, this microorganism passes through the urethra and access to the bladder. The contact to these sites is extremely facilitated by motility. P. mirabilis is a flagellar peritrichious bacterium. This microorganism presents swarming motility ability. This phenomenon occurs on 1.5% of agar surface and describes flagellum-dependent movement across the surface, resulting a characteristic bull's eyes pattern [3]. Swarming is important to P. mirabilis uropathogenesis. When this microorganism

presents swarmer cells form, the expression of virulence is increased [13].

4 Toxins

4.1 Hemolysin

Hemolysin is a toxin that inserts into target eukaryotic cell membranes forming a pore, causing the efflux of ions and subsequent cell damage [14]. Hemolysin facilitate bacterial spread within the kidney and development of pyelonephritis during ascending UTIs. The hemolysin genes of P. mirabilis is a two-partner secretion system (hpmA and hpmB). HpmB transports and activates HpmA. HpmA is found in the periplasm, while HpmB is probably found in the outer membrane to be located, participating in the secretion process of HpmA [15]. The role of the toxin as a virulence factor is not yet completely understood. HpmA presents cytotoxic activity onto cultured human renal proximal tubular epithelial cells [16]. However, in mice model of uropathogenic infection, no difference in colonization between the wildtype strain and the hpmA mutant was observed [1990]. Probably, this hemolysin is not as active during in vivo infection or the activity of other virulence factors masks its contribution.

4.2 Proteus toxic agglutinin (Pta)

Alamuri and Mobley [18] isolated and identified Pta from an isolate of uropathogenic P. mirabilis. They characterized this protein as outer-membrane autotransporter that mediates cell–cell aggregation and also contains a catalytically active α-domain capable of lysing kidney and bladder cells. P. mirabilis negative pta gene had reduced pathology as well as, a significant colonization defect in the bladder, kidneys and spleen [18], [19].

5 Enzymes

5.1 Urease

Urease is very important in P. mirabilis pathogenesis. This enzyme catalyze the formation of kidney and bladder stones or to encrust or obstruct indwelling urinary [20]. The urea-inducible urease gene cluster (ureRDABCEFG) encodes a multimeric nickel-metalloenzyme that hydrolysing urea to ammonia and carbon dioxide, thereby increasing the pH and facilitating the precipitation of polyvalent ions in urine (stone formation). This pH alteration is important during P. mirabilis catheter colonization, facilitating the bacterial adherence and formation of biofilm incrustation [20], [21]. Stone formation is a hallmark of P. mirabilis infection, supplying a number of advantage including, the host immune system protection, blockage of the ureters, ammonia toxicity to host cells, and direct tissue damage. These facts lead to a protective and nutrient-rich environmental niche for the microorganism.

TABLE 1
VIRULENCE FACTORS OF P. MIRABILIS

FACTOR	EFFECT
MR/P	Adhesin/ Imunne evasion
UCA/NAF	Adhesin
ATF	Adhesin
PMF	Adhesin
PMP	Adhesin
Hemolysin	Toxin
Proteus toxic agglutinin	Toxin
Flagella	Motility/ Imunne evasion
Urease	Enzyme
Quorum sensing	Cell-cell communication
ZapA	Imunne evasion

6 Quorum sensing

Cell-cell communication is utilized by several bacteria species to sense population density and coordinate gene expression [22]. P. mirabilis carries a luxS homologue and produces AI-2. However, this quorum sensing system do not affect swimming or swarming motility, swarmer cell differentiation, or virulence in vitro study [23]. However, AI-2 produced by P. mirabilis might influence gene expression in other species that use this signalling molecule.

7 Immune evasion

The bacteria persistence in the host must evasion of innate and adaptive immune responses. P. mirabilis present several evasion mechanisms. P. mirabilis encodes a metalloproteinase (ZapA), that cleaves serum and secretory immuno-globulin A1 (IgA1), IgA2 and IgG. Walker et al., [24] demonstrated that zapA mutantion results in a dramatic decrease in the recovery of bacteria from the urine, bladder and kidneys. This microorganism has ability to vary expression of MR/P fimbriae and flagellin, thus tricking the immune system [6]. As already mentioned, the stone formation is characteristic of uropathogenesis of P. mirabilis. This event contribute to persistence by causing retention of urine, generating a reservoir of bacteria, preventing wash-out and evasion of immune system [25].

8 Conclusions

P. mirabilis is a bacteria well-suited to the host. The colonization of the urinary tract is accomplished through the expression of several virulence factors. These factors are related to the processes of adherence, toxicity, evasion and motility. Recently, new genomes of this bacterium were sequenced and future studies will help in the discovery of new factors.

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