

Prevalence and Role of Adhesion Genes in *Proteus Mirabilis*

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Abstract: This study aims to investigate the prevalence of these adhesion genes in *P. mirabilis* strains isolated from patients with UTIs. The research seeks to provide insights into the distribution and potential role of these virulence factors. Understanding the prevalence and molecular mechanisms of *mrpA* and *ZapA* could contribute significantly to the development of targeted therapies and preventive strategies against *P. mirabilis* infections. *Proteus mirabilis* is a significant opportunistic pathogen known for causing urinary tract infections (UTIs) and other infections, posing a considerable public health challenge. The pathogenicity of *P. mirabilis* is complex and multifactorial, attributed to a range of virulence factors that enable the bacterium to colonize, invade, and persist within host tissues. Among these, adhesion genes like *mrpA* and *ZapA* play a crucial role in facilitating attachment, biofilm formation, and immune evasion. The *mrpA* gene is integral to the pathogenesis of *Proteus mirabilis*. It encodes a major component of the MR/P fimbriae, which is essential for bacterial adhesion to host tissues, biofilm formation, immune evasion, and persistence in the urinary tract. By facilitating these processes, the *mrpA* gene contributes significantly to the virulence of *P. mirabilis* and its ability to cause complex urinary tract infections. Understanding the role of *mrpA* in the pathogenesis of *P. mirabilis* could aid in the development of targeted therapies to prevent and treat infections caused by this bacterium.

Keywords: Urinary Tract Infection, *Proteus Mirabilis*, Adhesion Genes, *Mrpa*, *Zapa*, Fimbriae and Protease.

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1. INTRODUCTION

Proteus mirabilis belonging to the Enterobacteriaceae family, is a gram-negative motile, bacillus. It is a highly significant opportunistic pathogen that can be found in soil, water, and mammalian intestinal tracts. Many previous studies have indicated that *P. mirabilis* is one of the main causes of urinary tract infections (UTIs) and the main infectious agent in patients with indwelling urinary catheters. *P. mirabilis* can cause wound and respiratory infections, bacteremia, and various infections (Kadhim, Kadhim, & Hameed, 2017; Sun *et al.*, 2020).

The pathogenicity of *P. mirabilis* is due to a number of virulence components. These components consist of the presence of fimbriae, unique outer membrane proteins, flagella, swarming motility, urease, and all the aforementioned virulence factors that help them attach to, colonize, and invade tissues, thus increasing pathogenicity. Biofilm formation exacerbates

the difficulty of *P. mirabilis* infection, as biofilms are identified as the most common cause of chronic and complicated infections. (Chakkour *et al.*, 2024).

Scientists discovered a connection in last years between the development of biofilms and various virulence factors in human isolates of *P. mirabilis*. Jansen *et al.*, as an example, found that *P. mirabilis*, an infection of the urinary tract, can create mannose-resistant Proteus-like fimbriae that can cause biofilm formation by facilitate the aggregation of the bacteria (Mirzaei, Habibi, Bouzari, & Asadi Karam, 2019).

Studying the virulence factors of *Proteus mirabilis* bacteria isolated from clinical samples is of great importance to public health, as these bacteria constitute a major burden on health systems in the world. Studying the virulence factors paves the way for finding solutions for them, as the virulence factors represent the

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strengths of this bacteria that have caused an increase in its pathogenicity (Danilo de Oliveira *et al.*, 2021).

P. mirabilis infection can lead to various clinical conditions, including (UTIs), wound infections, bloodstream infections, and respiratory tract infections. This infection can cause significant morbidity and, in severe cases, lead to life-threatening complications. *P. mirabilis* has been increasingly associated with antimicrobial resistance, limiting treatment options for infected individuals. The presence of virulence factors in these bacteria could contribute to their ability to evade host immune responses and withstand the effects of antibiotics (Jamil, Foris, & Snowden, 2023).

Proteases are essential not only for the virulence of *P. mirabilis* but also for its survival, especially in the urinary tract. The environment within the urinary tract is challenging for bacteria because they face powerful host defenses such as antibodies and antimicrobial peptides. Among the various proteases used by *P. mirabilis*, *ZapA* (mirabilysin) is a potent metalloprotease capable of efficiently degrading many host proteins *in vitro*. The ability of *ZapA* to degrade a variety of host proteins *in vitro* confirms its adaptability and underscores its importance in disrupting the host immune response (Chakkour *et al.*, 2024).

The *mrpA* gene is integral to the pathogenesis of *Proteus mirabilis*. It encodes a major component of the MR/P fimbriae, which is essential for bacterial adhesion to host tissues, biofilm formation, immune evasion, and persistence in the urinary tract. By facilitating these processes, the *mrpA* gene contributes significantly to the virulence of *P. mirabilis* and its ability to cause complex urinary tract infections. Understanding the role of *mrpA* in the pathogenesis of *P. mirabilis* could aid in the development of targeted therapies to prevent and treat infections caused by this bacterium (Debnath *et al.*, 2018; Herout *et al.*, 2023).

The study aims to investigate the prevalence and role of adhesion genes (such as *mrpA* and *ZapA*) in *Proteus mirabilis* strains isolated from patients with UTIs and associated with these infections and potentially aid in the development of targeted therapies.

2. LITERATURES REVIEW

2.1. Historical Aspect *Proteus Mirabilis*

The bacterium *Proteus* was first discovered by Hauser in 1885, who isolated it from feces, sewage, and decaying organic matter and named it *Proteus*, noting its pleomorphism (Drzewiecka, 2016). The genus *Proteus*, first described by Hauser in 1885, was later classified under the family Enterobacteriaceae. In the 1993 edition of Bergey's Manual of Determinative Bacteriology, *Proteus* was placed in Group 5, encompassing Gram-negative rod-shaped bacteria. This group includes the tribe Proteaeae, which comprises three genera: *Proteus*, *Providencia*, and *Morganella*. The 1913 edition of

Bergey's Manual identified five species within the genus *Proteus*: *P. mirabilis*, *P. vulgaris*, *P. rettgeri*, *P. inconstans*, and *P. morganii*. (El-Kady *et al.*, 2023; Jamil *et al.*, 2023). However, the classification was revised by Henriksen in 1951, who differentiated between the genera *Proteus* and *Providencia* based on biochemical tests, particularly the ability to produce the enzyme deaminase, which other members of the Enterobacteriaceae family do not produce (O'Hara, Brenner, & Miller, 2000).

Based on DNA hybridization studies, structural differences in certain proteins, and phenotypic characteristics, the species *Proteus rettgeri*, discovered by Rettger in 1913, was reclassified into the genus *Providencia*, becoming *Providencia rettgeri* (C. Yuan *et al.*, 2020). Similarly, *P. inconstans* was also transferred to the genus *Providencia* and divided into two species: *Providencia stuartii* and *Providencia alcalifaciens*. Additionally, *P. morganii* was reclassified into the genus *Morganella*, becoming *Morganella morganii*, based on its (G+C) content, which is 51%, higher than other *Proteus* species with 49%. According to the modern classification, the genus *Proteus* now includes five species: *P. mirabilis*, *P. vulgaris*, *P. penneri*, *P. hauseri*, and *P. myxofaciens*, based on biochemical interactions (O'Hara *et al.*, 2000).

2.2. General Characteristics of *Proteus.SPP*

These bacteria are described as gram-negative, short rods with diameters ranging from 0.3 to 1.0 micrometers and lengths from 0.6 to 6.0 micrometers (Abbott, 2011). They are motile and non-spore-forming. They possess a capsule and contain fimbriae as well as flagella. *Proteus* bacteria are oxidase-negative and urease-positive, producing hydrogen sulfide (H₂S) when grown on Kligler iron agar. They test positive for the methyl red test and negative for the Voges-Proskauer test (Schaffer & Pearson, 2015). They can produce phenylpyruvic acid when grown on media containing phenylalanine, due to the production of the enzyme phenylalanine deaminase. They are catalase-positive and, except for *P. vulgaris*, indole-negative. On MacConkey agar, *Proteus* colonies appear pale yellow due to their inability to ferment lactose, though they can ferment glucose, sucrose, and galactose. *Proteus* bacteria are characterized by their aerobic nature (Hou *et al.*, 2015).

P. mirabilis exhibits a phenomenon known as swarming, which is believed to enhance its ability to colonize the urinary tract. When inoculated into a nutrient broth, *P. mirabilis* differentiates from short, motile swimmer cells into elongated swarmer cells, which are twice the length of swimmer cells and covered with thousands of lateral flagella as shown in Figure 1. In solid culture media, these swarmer cells divide and swarm collectively at very high rates (Chakkour *et al.*, 2024).

P. mirabilis moves using peripheral flagella, which become apparent when the bacterium is grown on culture media, forming characteristic rings on agar surfaces. Colonies are rarely observed on blood or nutrient agar due to the swarming motility of *P. mirabilis*. The bacteria rapidly migrate across the agar

surface, forming concentric waves of dense growth that eventually cover the entire plate. This swarming behavior is influenced by environmental factors, including the presence of specific amino acids and peptides (Bonnet, Lagier, Raoult, & Khelaifia, 2020).

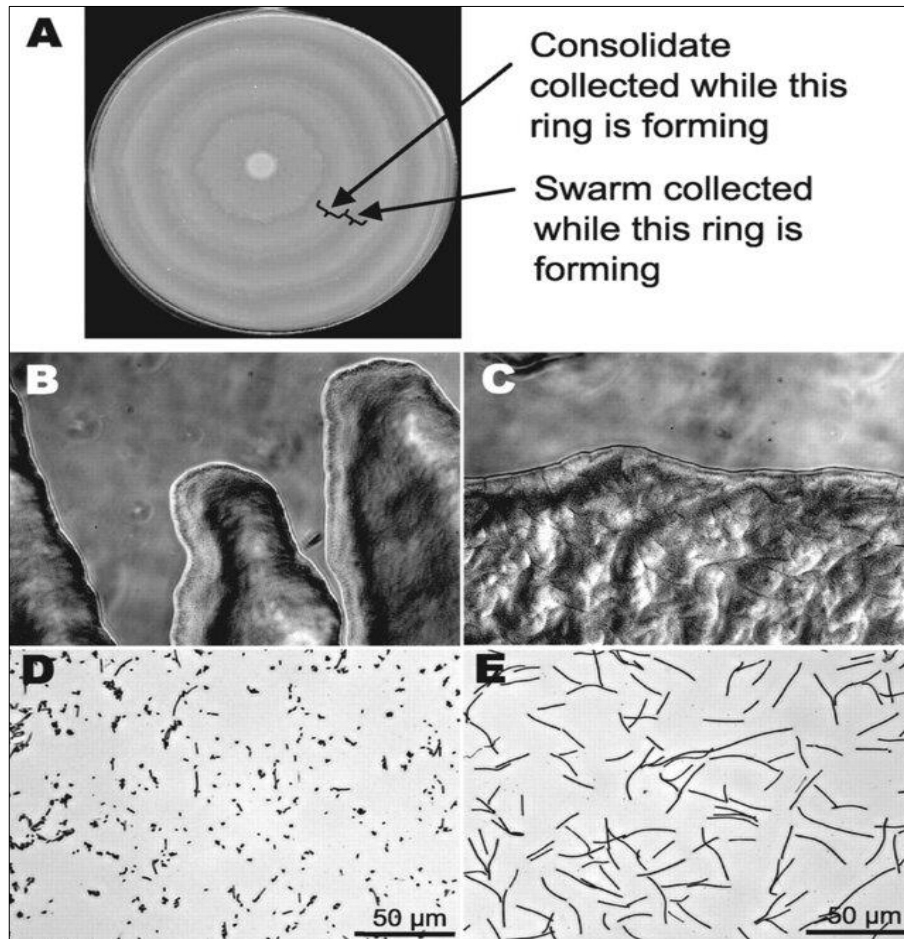


Figure 1: (A) *P. mirabilis* swarm plate with time points indicated for sample collection for microarray analysis is shown. The edge of a newly forming consolidation ring exhibits finger-like projections (B), while the edge of an actively swarming front appears smooth (C). Gram staining of bacteria from the edge of a consolidating colony reveals vegetative cells (D) (Pearson, Rasko, Smith, & Mobley, 2010)

2.3. Pathogenicity of *P. Mirabilis*

P. mirabilis is one of the most pathogenic bacteria for its role in causing urinary tract infections (UTIs), especially in people with complicated UTIs or people with structural abnormalities within the urinary tract (Jamil *et al.*, 2023). Several virulence components contribute to its pathogenicity. *Mirabilis* possess fimbriae, which can be hair-like systems on their outer membrane that facilitate attachment to host tissues. These fimbriae, composed of mannose-resistant Proteus-like (MR/P) fimbriae, allow microorganisms to contact epithelial cells. Lining of the urinary tract. This association is necessary for colonization and increased pathogenicity (Chakkour *et al.*, 2024).

P. mirabilis also multiple virulence factors, including its ability to adhere to host tissues using pili,

its motility via flagella, and its production of toxins and enzymes such as hemolysins and bacteriocins, which aid in evading the host's immune system (Zegadło *et al.*, 2023).

Another key aspect of virulence is the ability of bacteria to move, which is enabled by flagella as shown in Figure 2. The flagella of *P. mirabilis* allow it to move up and down the urinary tract and move from the bladder to the kidneys. This movement enables it to increase its pathogenicity. *Mirabilis* additionally produces urease, an enzyme that hydrolyzes urea into ammonia and carbon dioxide (Scavone *et al.*, 2023).

This enzymatic activity results in an increase in urine pH, making it more alkaline. An alkaline environment encourages the formation of crystals and

kidney stones, which may obstruct the urinary tract and aggravate infections. Furthermore, *P. mirabilis* can produce contamination that contributes to tissue damage and the spread of infection (Duque-Sanchez, Qu, Voelcker, & Thissen, 2024).

Hemolysin, a pore-forming toxin, can lyse host cells and disrupt cell functions (F. Yuan *et al.*, 2021). Agglutinins (Pta) are some other toxins that damage host cell membranes and contribute to tissue irritation and injury. The ability of *P. mirabilis* to form biofilms is a major aspect of its pathogenicity. Biofilms are complex collections of microorganisms encased in a defensive

matrix. These biofilms can adhere to surfaces, including catheters and clinical devices, making them difficult to remove (Bunyan & Albakery, 2020).

The biofilm matrix protects microorganisms from antibiotics and the host immune response, resulting in persistent and recurrent infections. A complex interaction of several virulence components, which include fimbriae, flagella, urease, fouling, and biofilm formation. These elements allow microorganisms to attach to host tissues, colonize the urinary tract, evade the immune system, and cause damage to host cells and tissues (Wasfi, Hamed, Amer, & Fahmy, 2020).

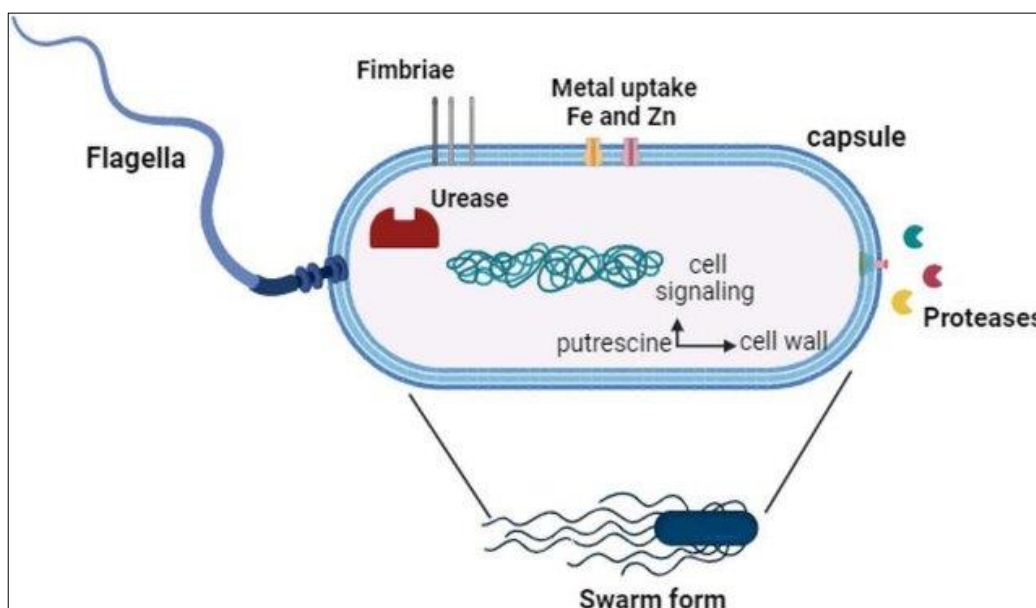


Figure 2: *Proteus mirabilis* with the most prominent factors that increase its pathogenicity (Chakkour *et al.*, 2024).

Internalization of *P. mirabilis* by bladder epithelial cells has been directly demonstrated in vitro using a hemolysin (*hpmA*) mutant to avoid confounding from the effects of the cytolytic toxin. In these experiments, it was determined that *P. mirabilis* utilizes the AipA autotransporter for internalization into bladder cells (Filipiak *et al.*, 2020).

In addition to internalization, *P. mirabilis* is capable of lysing bladder epithelial cells using a combination of the Proteus toxic agglutinin (Pta) and hemolysin. In the murine model of ascending UTI, *P. mirabilis* invades bladder epithelial cells as early as 30 min post inoculation, which may provide transient protection from the immune response and an intracellular niche for initial replication and survival. However, intracellular bacteria are uncommonly observed at later times post inoculation, and *P. mirabilis* appears to instead form large, extracellular clusters within the bladder lumen and adjacent to the urothelium after this initial invasion phase rather than establishing the intracellular communities that are characteristic of uropathogenic *E. coli* (Filipiak *et al.*, 2020).

2.4. Virulence Factor of *Proteus Mirabilis*

2.4.1. Hemolysin Production

Hemolysin synthesis is a major virulence component in *P. mirabilis*. These bacteria produce a form of hemolysin referred to as *HpmA*, which is a calcium-dependent, pore-forming cytotoxin. The mechanism of movement involves insertion of *HpmA* into the outer membrane of the cell, mainly leading to pore formation (Bunyan & Albakery, 2020).

These pores disrupt the integrity of the moving membrane, causing ionic imbalances, especially the influx of sodium ions (Na⁺). This disturbance ends in the destabilization of the mobile and in the long-term decay of the mobile. This hemolytic character of *HpmA* contributes to pore formation (Mirzaei *et al.*, 2019). The pathogenicity of *P. mirabilis* can be traced back to several ways. They can instantly damage host tissues, leading to irritation and tissue injury. In addition, it can provide drainage of cell contents from the decomposing cells of bacteria, promoting their growth and survival. Furthermore, *HpmA* can disrupt host immune responses by focusing on harmful immune cells (Bunyan & Albakery, 2020).

2.4.2. Capsule Formation

Capsule formation is one aspect of the massive virulence that contributes to the pathogenicity of *P. mirabilis*. The capsule, a sticky layer composed of polysaccharides, envelops the mobile bacterial cell and performs several important adhesion roles (Palusiak, 2022). The capsule allows *P. mirabilis* to attach to host tissues and surfaces, such as catheters and clinical devices. This is vital for colonization and pathogenicity in the urinary tract. It also works on immune evasion as the capsule acts as a shield, protecting the bacteria from the host's immune system (Gmiter & Kaca, 2022).

It also protects them from phagocytosis, which is the method by which immune cells engulf and destroy invading pathogens. This allows *P. mirabilis* to evade immune surveillance and remain in the host. The capsule also has a role in protection, as the capsule provides protection against many environmental stressors, such as antimicrobial peptides produced by the host as a protection mechanism (F. Yuan *et al.*, 2021).

In addition, it allows bacteria to resist drought and maintain their ability to survive in difficult conditions. The capsule also has an important role in antibiotic resistance, as the presence of the capsule can contribute to antibiotic resistance in *P. mirabilis*. It can act as a barrier that hinders the penetration of antibiotics and reduces their effectiveness in killing bacteria. The *P. mirabilis* capsule is a complex form with antigenic properties. They can cause the production of anti-capsular antibodies by the host's immune system. These antibodies can be used for rapid detection. Of *P. mirabilis* infection and could provide potential targets for vaccine development (Helmy *et al.*, 2023; Wasfi *et al.*, 2020).

2.4.3. Biofilm Formation

Biofilm is an ordered accumulation of microorganisms residing inside an extracellular polymeric matrix that they create and that is irreversibly bound to the fetish or living surface and can not be removed until rinsed immediately (Jamal *et al.*, 2018). Biofilm formation is a significant virulence mechanism in the pathogenesis of many medically important bacterial pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus spp.*, and *Escherichia coli*. Vaginitis, colitis, conjunctivitis, gingivitis, urethritis, and otitis are only a few of the diseases that have been linked to biofilm infections. In reality, biofilms are thought to be the direct cause of 80% of all microbial infections in humans. The above is a biofilm-related infection that is of special medical significance (Verderosa *et al.*, 2019).

Implanted surgical instruments are another important consideration when it comes to biofilm-related infection. Microbial adhesion resulting in biofilm formation on implanted medical devices is a common occurrence and can lead to serious illness and death. These implanted medical devices, intravascular

catheters, vaginal catheters, pacemakers, heart valves, stents, and orthopedic implants are also widely used to save lives, but when colonized by bacterial biofilms, they can pose a serious health danger (Paluch *et al.*, (2020).

2.5. Virulence Genes of *Proteus Mirabilis*

2.5.1. Ambient Temperature Fimbriae (*atfA*)

The *atfA* gene in *Proteus mirabilis* is one of the most important virulence factors. It encodes the *AtfA* protein, a transcriptional regulator that belongs to the AraC/XylS family. *AtfA* plays an important role in controlling the expression of genes related to other virulence factors such as biofilm formation, swarm movement, and various virulence mechanisms. Studies have demonstrated that mutations or deletions within the *atfA* gene can cause attenuated virulence in *P. mirabilis* (Sun *et al.*, 2020).

These mutants show reduced biofilm formation, impaired swarming motility, and decreased resistance to antimicrobial agents. The *atfA* protein regulates the expression of many genes involved in these virulence traits, including genes encoding fimbriae, flagella, and other ground structures. The *atfA* gene is considered one of the strengths of *P. mirabilis*. It contributes to the ability of bacteria to adapt and survive in difficult environments and unsuitable conditions, including the urinary tract, where they encounter host defenses and antimicrobial agents (Sanches *et al.*, 2019).

2.5.2. Mannose-Resistant/Proteus-Like Fimbriae *mrpA*

The *mrpA* gene in *Proteus mirabilis* is a critical virulence factor responsible for the production of mannose-resistant Proteus-like (MR/P) fimbriae. These fimbriae are hair-like appendages on the bacterial surface that mediate adherence to host tissues and play a vital role in the initiation and progression of urinary tract infections (UTIs) (Himplsl, Pearson, & Mobley, 2019).

The MR/P fimbriae encoded by the *mrpA* gene enable *P. mirabilis* to attach specifically to mannose-resistant receptors present on the uroepithelial cells lining the urinary tract. This adherence is crucial for the successful colonization of the urinary tract and the establishment of infection (Durgadevi *et al.*, 2020).

The *mrpA* gene also contributes to the formation of biofilms, which are complex communities of bacteria encased in a protective matrix. Biofilms enhance the persistence of *P. mirabilis* within the urinary tract, making it difficult to eradicate with antibiotics and host immune responses (Durgadevi *et al.*, 2020).

The MR/P fimbriae can interfere with host immune mechanisms, allowing *P. mirabilis* to evade detection and clearance by the immune system. This contributes to the bacterium's ability to persist and cause chronic or recurrent UTIs (Pearson, 2019).

The *mrpA* gene is part of a complex regulatory network that controls the expression of other virulence factors in *P. mirabilis*. This coordinated regulation ensures the optimal expression of virulence traits at different stages of infection (Sun *et al.*, 2020).

2.5.3. Proteus Mirabilis Fimbriae (*pmfA*)

P. mirabilis fimbriae (*pmfA*) are filamentous appendages on the bacterial surface that play a crucial role in its virulence. The *pmfA* gene cluster is responsible for encoding the structural and assembly components of these fimbriae (Zunino *et al.*, 2003). Pmf fimbriae contribute to the pathogenicity of *P. mirabilis* in several ways for instance adherence and colonization *pmfA* facilitate the attachment of the bacteria to host tissues, specifically to receptors on epithelial cells lining the urinary tract. This adherence is essential for successful colonization and the establishment of infection (Zunino *et al.*, 2003).

Also have an important role in biofilm formation are involved in the initial stages of biofilm development. They promote the aggregation of bacterial cells and their attachment to surfaces, contributing to the formation of the biofilm matrix (Sun *et al.*, 2020).

pmfA may also play a role in the invasion of host cells by *P. mirabilis*. They can interact with host cell receptors and trigger signaling pathways that facilitate bacterial entry (Armbruster, Mobley, & Pearson, 2018).

pmfA can interfere with host immune responses. They can inhibit phagocytosis, the process by which immune cells engulf and destroy bacteria. This allows *P. mirabilis* to evade immune surveillance and persist within the host (Armbruster *et al.*, 2018).

The expression of the *pmfA* gene cluster is regulated by various environmental factors and gene regulatory systems within *P. mirabilis*. This coordinated regulation ensures the optimal expression of Pmf fimbriae and other virulence factors at different stages of infection (Debnath *et al.*, 2018).

2.5.4. Metalloprotease Zinc-Associated Protein (*zapA*)

Metalloprotease *ZapA* is an important virulence factor of uropathogenic *Proteus mirabilis*. While *ZapA* has the ability to degrade host immunoglobulins (Igs), the dramatic attenuation of virulence in *ZapA* mutants suggests that this enzyme may have a broader spectrum of activity (Belas, Manos, & Suvanasuthi, 2004).

Swarm cell formation, which is important in the pathogenesis of this organism, results in the upregulation of many *P. mirabilis* virulence factors, including *ZapA*. This appears to be influenced by the ability of *P. mirabilis* to sense surfaces, and, not surprisingly, swarm cell formation is also seen in biofilm formation in artificial urine, which may explain

the link of pathogenesis to catheterization and anomalies in the urinary tract, where biofilm formation will be encouraged (Belas *et al.*, 2004).

3. CONCLUSIONS

In conclusion, *Proteus mirabilis* is a significant opportunistic pathogen responsible for various infections, particularly in the urinary tract. The pathogenicity of *P. mirabilis* is attributed to a range of virulence factors including fimbriae, flagella, urease, and biofilm formation. Adhesion genes, such as *mrpA* and *ZapA*, play a crucial role in the bacterium's ability to adhere to host tissues, evade immune responses, and establish persistent infections.

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