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Review article

Adhesion of *Stenotrophomonas maltophilia* to Biotic and Abiotic Surfaces and Role of Flagella in Bacterial Adhesion

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ABSTRACT

The bacterial adhesion to the biotic and abiotic surfaces represents the first step in infection and contributes to increasing the pathogenicity of bacteria. In the current review, we have shed light on the ability of *Stenotrophomonas maltophilia* to adhere to biotic and abiotic surfaces and the role of this adhesion in increasing the virulence of this bacteria and its ability to cause infectious diseases. The adhesion of *S. maltophilia* to abiotic surfaces contributes to the bacteria's resistance to the wild spectrum of antibiotics in addition to evading the body's immune response during biofilm formation. Bacterial appendages such as flagella and pili play an important role in adhesion to biotic and abiotic surfaces. Studies have shown the role of the flagella of S. maltophilia in adhesion to biotic and abiotic. The current study also showed the role of pili of *S. maltophilia* and bacterial outer membrane proteins in adhesion to the surfaces. The adhesion of bacteria to biotic surfaces occurs through the attachment of bacterial appendages to receptors located on the surfaces of living cells. The mechanism adopted by *S. maltophilia* to adhere to biotic surfaces is through binding to specific receptors on the surface of living cells or by attaching to mucus, especially in the respiratory tract. As for adhesion to abiotic surfaces, it depends on the hydrophobic forces as well as the electrical charges and the van der Waals force. Adhesion of *S. maltophilia* to the surfaces is considered one of the mechanisms used by bacteria to resist antibiotics and cause infectious diseases. The increased ability of S. maltophilia to adhere to surfaces has contributed to the increase in the pathogenicity of this bacteria in recent years.

Keywords: Abiotic surfaces, Adhesion, Biotic surfaces, Flagella, *Stenotrophomonas maltophilia*.

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1. INTRODUCTION

Stenotrophomonas maltophilia is a Gram-negative, opportunistic pathogen that can cause a variety of infections, including pneumonia, urinary tract infections, and bloodstream infections. It is particularly common in healthcare settings and in patients with weakened immune systems [1]. Previous studies have reported the ability of both clinical and environmental *S. maltophilia* isolates to adhere to abiotic surfaces [2]. This is non-specific adhesion as the interaction occurs between the bacterial surface and synthetic surface without involving the participation of specific receptors. However, information about the ability of *S. maltophilia* to adhere to biotic surfaces is scanty in the literature. This kind of adhesion is called specific adhesion as the interaction occurs between specific receptors on bacterial surface and biotic surface. For example the interaction between

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the bacterial flagellin and TLR5 on airway epithelial cells [3]. The adhesion takes place in two steps, primary and secondary adhesion [4]. Primary adhesion constitutes a serendipitous contact between a conditioned surface and a planktonic microorganism. This stage is reversible and is dictated by several physiochemical variables that define the interaction between the bacterial cell surface and the conditioned surface of interest [4]. The second stage of adhesion is the anchoring or locking phase and employs molecularly mediated binding between specific adhesins and the surface [4]. At this point, loosely bound organisms consolidate the adhesion process by producing exopolysaccharides that are complex with surface materials and/or receptor-specific ligands located on pili and flagella, or both. For example, flagella plays a crucial role in bacterial attachment to epithelial cells in bacteria like *Pseudomonas aeruginosa, B. cepacia, and Stenotrophomonas maltophilia* [5]. At the conclusion of the second stage, adhesion becomes irreversible in the absence of physical or chemical intervention, and the organism is attached firmly to the surface [6]. Flagella are long, whip-like appendages that allow bacteria to move [1]. They are also involved in other bacterial functions, including adhesion to surfaces. Flagella are composed of a protein called flagellin, which can interact with a variety of host molecules, including mucins and proteins on the surface of host cells. Studies have shown that flagella play an important role in *S. maltophilia* adhesion to a variety of surfaces, including host cells, abiotic surfaces, and other bacteria. For example, one study found that flagella were essential for *S. maltophilia* adhesion to mouse tracheal mucus [7]. Another study found that flagella were involved in *S. maltophilia* adhesion to abiotic surfaces, such as glass and plastic [8].

Flagella can also promote *S. maltophilia* biofilm formation. Biofilms are communities of bacteria that are attached to surfaces and enclosed in a matrix of extracellular material. Biofilms are difficult to treat with antibiotics and can be a source of chronic infections. The precise mechanism by which flagella promote *S. maltophilia* adhesion is not fully understood. However, it is thought that flagellin may interact directly with host molecules or with other bacterial adhesins [8]. Flagella may also play a role in generating the force required for bacteria to attach to surfaces. Further research is needed to fully understand the molecular mechanisms involved and to develop new strategies for preventing and treating *S. maltophilia* infections.

2. ADHESION

Over the years significant work has been done to investigate the process of bacterial adhesion to tissues and biomaterial surfaces but still many questions remain unanswered. The research on bacterial adhesion and its significance is a large field covering different aspects of nature and human life such as marine science, soil and plant ecology, the food industry, and most importantly the biomedical field. The adhesion of bacteria to human tissue surfaces and implanted biomaterial surfaces is an important step in the pathogenesis of infection [9]. Adhesion of bacteria to solid surfaces has been described as a two-phase process including an initial, instantaneous, and reversible physical phase (phase 1) and time-dependent and irreversible molecular and cellular phase (phase 2) [6]. Bacterial adhesion to surfaces includes (i) an initial attraction of the cells towards a surface due to van der Waals attraction forces, Brownian motion, gravitational forces, electrostatic charges, and hydrophobic interactions [6], (ii) molecular and cellular interactions by use of microbial surface polymeric structures such as capsules, fimbriae or pili, exopolysaccharide EPS and Flagella [10].

Specific interaction between microbial surface ligands or adhesins and host receptors, influence the distribution of microbes at the site of infection and help them to gain access to host tissue. Microbial cells are able to adhere to surfaces and through an exo-polymeric matrix they establish microbial communities known as biofilms [6]. In fact, the host immune system in general is capable of rapidly killing the non-adherent bacteria but adhesion is one such process used by bacteria to get rid of the immune system by forming biofilm. The slow growth rate observed in biofilms and/or transport limitations of nutrients, metabolites, and oxygen between the surface and the interior of the biofilm could be responsible for an increased antibiotic resistance over planktonic cells [10].

Cell surface hydrophobicity may influence the rate and the extent of microbial attachment. The hydrophobicity of the cell surface is important in adhesion because hydrophobic interactions tend to increase with an increasing non-polar nature of one or both surfaces involved, i.e., the microbial cell and the adhesion surface [11].

3. APPENDAGES AND ADHESION

3.1. Pili

Pili or fimbriae are found in many Gram-negative bacteria. They are fine, filamentous appendages, also of protein, 4–35 nm wide and up to several micrometers long. These structures are usually straight. Their only known general function is to make cells more adhesive since bacteria with pili can adhere strongly to other bacterial cells and inorganic particles. Nevertheless, they are not always involved in the attachment process even if they are present. pili and pilus-associated structures have been shown to be important for the adhesion and colonization of surfaces, probably by overcoming the initial electrostatic repulsion barrier that exists between the cell and the substratum [12]. The role of pili in host cell adherence and tissue tropism has been well established from studies of gram-negative bacteria, which contain distinct types of pili, namely type I pili, Pap pili, type IV pili, and curli pili. [13]. McCutcheon et al. (2018) reported that the major pilin subunit, pilA, was identified in *S. maltophilia* D1585, and was subsequently used to identify the pilA ortholog in *S. maltophilia* 280 [14]. Wang et al. (2020) described the outer membrane of *S. maltophilia* and its role in stimulating the immune response in the epithelial cells.

3.2. Outer-membrane proteins (OMPs)

Many studies emphasize that OMPs play a crucial role in bacterial adhesion to different surfaces. A family of variably expressed outer-membrane proteins (Vomp) mediate adhesion and auto-aggregation in *Bartonella quintana* [15]. The porin F (OprF) from the outer membrane of *P. aeruginosa* was identified as an adhesin for human alveolar epithelial (A549) cells [16]. Wang et al. (2020) showed the role of *S. maltophilia* outer membrane protein in inducing epithelial cell apoptosis via mitochondrial pathways [17].

3.3. Flagella

The most common and best-studied of all prokaryotic motility structures is the bacterial flagellum. Composed of over 20 protein species with approximately another 30 proteins required for regulation and assembly, it is one of the most complex of all prokaryotic organelles. Well understood in its own right as a motility structure, it has become a model system for

type III secretion systems in general [18]. The bacterial flagellum is a rotary structure driven by a motor at the base, with the filament acting as a propeller. The flagellum consists of three major substructures: the filament, the hook, and the basal body. The filament is typically about 20 nm in diameter and usually consists of thousands of copies of a single protein called flagellin [19]. Less commonly the filament is composed of several different flagellins. At the tip of the flagellum is the capping protein. Hook-Associated Protein 2 (HAP2) connects the filament to the basal body. The junction of the hook and filament requires the presence of a small number of two hook-associated proteins called HAP1 and HAP3. The basal structure consists of a rod, a series of rings, the Mot proteins, the switch complex, and the flagellum-specific export apparatus [20]. The rings anchor the flagellum to the cytoplasmic membrane (MS ring), the peptidoglycan (P ring), and the outer membrane (L ring). Gram-positive bacteria have flagella that lack the P and L rings [21].

The engine is powered by proton motive force. Motility protein A (MotA) and motility protein B (MotB) proteins form a channel through which the protons that power the rotation of the flagellum flow. Flagellin is a protein that arranges itself in a hollow cylinder to form the filament in the bacterial flagellum. It has a mass of about 30,000 to 60,000 Dalton. The structure of flagellin is responsible for the helical shape of the flagellar filament which is important for its proper function. The flagellin variable domain protrudes outwards and stacked together with other flagellin monomers, forms the external surface of the filament [22]. The surface exposed variable domain of the flagellin is antigenically diverse and forms the basis of a wide range of typing methods exploiting the diversity of the structural difference at the protein level for strain identification. The diversity in flagellin structure has been used as a new strategy for strain identification in *Clostridium botulinum* [23]. Flagella are often involved in pathogenesis, with a role in motility, adhesion, and in some cases the secretion of virulence factors and stimulate the pro-inflammatory immune response [24].

4. *S. maltophilia* FLAGELLA

A polytrichious flagellated *S. maltophilia* is one of the emerging pathogens. Several research that followed the characterization of the flagella and flagellin of *S. maltophilia* are available in the literature. By using a centrifugation technique, Montie and Stover isolated flagella from many pseudomonas species in 1983, including *P. maltophilia* strain B69 (now known as *S. maltophilia*) [25]. They discovered that B69 generated a flagellin with a molecular mass of 33 kDa. They discovered that *P. maltophilia* bacteria were not agglutinated by anti-sera directed against the flagella of *P. aeruginosa* or *P. cepacia*, indicating that there is no antigenic cross-reactivity between these flagella. There hasn't been any more biochemical characterization of *S. maltophilia* flagella done. Although they employed several techniques for purification, De Oliveira-Garcia et al. (2002) documented the purification and characterization of *S. maltophilia* flagella. A 38-kDa flagellin component makes up the flagella generated by *S. maltophilia* strains. The examination of the N-terminal amino acids revealed the polypeptide's identification. To study the production of flagella in a group of clinical isolates, researchers also raised specific antibodies. Using electron microscopy, they discovered that some organisms had only one polar flagellum, while others had multiple flagella structures. The flagella filaments were about 45 nm wide and >15 m long [2]. By using anti-flagellin antibodies or flagellin as adhesion inhibitors, Zgair and Chhibber (2009) demonstrated that the participation of flagella in the adhesion process was assessed. This was accomplished by purifying flagellin C from a clinical wild-type isolate (Sm2) that exhibited the greatest *in vitro* adhesion. The molecular weight of the pure preparation was 42 kDa on SDS-PAGE, and immunoblotting using rabbit antisera produced against this preparation verified its purity. By either pretreating mouse trachea or HEp-2 cells with pure flagellin or by treating bacteria with anti-flagellin, the receptors were inhibited. The involvement of flagella in bacterial attachment to biotic surfaces was validated by the decreased bacterial adhesion in the presence of pure flagellin and flagellin antisera. Antiserum, however, was more successful in decreasing adhesion, most likely as a result of its dual mechanism of action. It not only decreased the adhesins' ability to connect to certain receptors on the flagella, but it also prevented *S. maltophilia* from moving around. The effect of antibodies on bacterial motility was demonstrated by the bacterial colony's incapacity to spread across antiserum-containing agar [26]. The same researcher also showed that *S. maltophilia* can cling to mouse tracheal mucus and that flagella is crucial to this process. To corroborate this conclusion, more research with genetically specified mutants deficient in flagella is required [7].

5. FLAGELLA IN BACTERIAL ADHESION

Flagella have been implicated in the adherence to mucous and cells. Its role in the colonization of *P. aeruginosa* [27], and *Burkholderia pseudomallei* [28] were demonstrated. Furthermore, it has been shown that flagella contributes to the invasiveness of *Proteus mirabilis* [29]. The role of flagella in adherence of *P. aeruginosa* and *E. coli* on abiotic surfaces has been documented [30, 31]. In addition, the role of flagella in the formation and development of biofilms has been investigated in different bacterial species [32]. Flagella help bacteria to attach to biotic and abiotic surfaces in many ways. These include i, Motility: The motility of *B. cepacia* may be particularly important for initiation of contact between bacteria and epithelial cells and may promote adherence to the airway epithelia of the lung and subsequently invasion of deeper tissue. Additionally, motility may allow *B. cepacia* to penetrate the viscous mucous that covers the airway [33]. ii, Biofilm formation. iii, Flagellin protein is directly linked to toll-like receptors TLR2, TLR5, and asialoGM1 [34]. Several investigators have studied the adhesion of bacteria to different biotic surfaces. These included different kinds of cell lines such as human airway epithelial cells (1HAEo− cells and 16HBE cells) [35]. HEp-2 cell line has been cultured to study the adherence behavior of *S. maltophilia* on epithelial cells [25, 36].

6. ADHESION TO THE SURFACES

The bacterial adhesion on the surfaces takes place in two ways, first monolayer formation on the surfaces and second bacterial aggregation (flagellated bacteria). The wild-type parent strain first forms a surface monolayer of cells through primary adhesion. Monolayer cells then “walk” via twitching motility to form cellular aggregates on surfaces that eventually differentiate into microcolonies [6]. Taken together, these findings indicate that flagellar motility is required for primary adhesion, and type IV pili are essential for cellular aggregation [6]. It has been suggested previously that flagellar motility might be necessary to bring cells into close proximity to a surface [37]. The association between motility and biofilm development has been noted with other organisms [38]. In general, the initial step of biofilm formation is the adhesion of the microorganisms to surfaces by unspecific physicochemical interactions or by specific interactions [39]. More than 67 years after the first report

on biofilms, they are still a concern in a broad range of areas, specifically in the food, environmental, and biomedical fields [40]. It is a natural tendency of microorganisms to attach to wet surfaces, to multiply, and to embed themselves in a slimy matrix composed of extracellular polymeric substances (EPS) that they produce, forming a biofilm. A biofilm is a population of cells growing on a surface surrounded by an extracellular polysaccharide matrix. They are mushroom-like structures with polysaccharide-enclosed microorganisms. Biofilm cells are more complex and have different characteristics compared to planktonic cells [6]. One of the most important features of biofilms is their resistance to antimicrobials and components of the host immune system. Studying the metabolic pathways of Stenotrophomonas maltophilia could uncover new metabolic activities that may be useful in inhibiting the growth and biofilm formation of this pathogen, which is a prominent opportunistic pathogen that often forms biofilms during infection and has high antimicrobial resistance [41]. Since biofilms offer an optimum surrounding for the cells, bacteria prefer being in a closely integrated community over a planktonic state.

The adhesion of bacteria to different types of plastics was systematically investigated, and the results showed that the number of bacteria that adhered to polyethylene and polyvinyl chloride surfaces was much greater than that attached to polypropylene hydrophobicity terephthalate, with surface hardness being the key factor dominating the adhesion of bacteria onto plastic surfaces, providing insights to assess the fate and transport of different types of plastics in real environments [42]. Hydrophobicity is thus a significant determinant of adhesion and biofilm formation on polystyrene surfaces in *S. maltophilia* [43]. *S. maltophilia* forms biofilm on abiotic surfaces and both clinical and environmental isolates produce biofilm with equal efficiency [44]. The ability to adhere to biotic and abiotic surfaces as well as its ability to resist a wide spectrum of antibiotics had made this organism in the decade as one of the important bacteria responsible for nosocomial infections [44]**.** There are many mechanisms of *S. maltophilia* adhesion to abiotic surfaces and biofilm formation. Jucker *et al*. (1996) reported that nonspecific adhesion and biofilm formation by *S. maltophilia* to glass and Teflon may be attributed to the net positive surface charge of the bacteria [45]. As with a variety of microorganisms, other surface determinants may confer the adhesive attributes necessary for *S. maltophilia*-specific adhesion. The adhesion of bacteria to the artificial solid surface is governed mainly by long-range van der Waals and electrostatic interactions between the solid surface and the bacterial cell. While van der Waals forces are generally attractive, the usually negative charge of bacteria and solid surfaces leads to electrostatic repulsion. But the clinical isolate *S. maltophilia* 70401, which is, at physiological pH, positively charged so the interaction is an attraction between sold surfaces and *S. maltophilia*. De Oliveira-Garcia *et al*. (2003) found the role of pili in some clinical isolates of *S. maltophilia* participated in bacterial adhesion to abiotic and biotic surfaces. They also found the pili participated in biofilm formation by *S. maltophilia* on abiotic surfaces. The involvement of flagella in *S. maltophilia* adhesion to different kinds of surfaces and biofilm formation has been described by other investigators [46, 2].

7. CONCLUSION

The current study demonstrated the clear role of flagella in the adhesion of different types of bacteria, especially *S. maltophilia*, to biotic and abiotic surfaces. The mechanism adopted by *S. maltophilia* bacteria to adhere to biotic surfaces is through binding to specific receptors found on the surface of living cells or by attaching to mucus, especially in the respiratory tract. As for adhesion to abiotic surfaces, it depends on the hydrophobic forces as well as the electrical charges and the van der Waals force. Adhesion of *S. maltophilia* to the surfaces is considered one of the mechanisms used by bacteria to resist antibiotics and cause infectious diseases.

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Conflict of interest

The authors declare that they have no conflict of interests.

Ethical Approval

This review was approved by the Scientific Committee of the Ministry of Higher Education, Baghdad, Iraq (No 173, 2022).

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