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Shewanella: Pathogenicity Classification and its Relationship with Biofilm Formation

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Abstract
This narrative review collecting the data about the rare pathogenic bacterium called *Shewanella* and due to its clinical importance writing about it considered good idea to highlight some of its characters, classification, distribution, the infection and diseases related with it. It's clear from the data collected that this pathogenic bacterium considered a direct agent for clinical infection (skin, ear, nose, throat, soft tissue, chest, and abdominal cavity infection The study confirmed that *Shewanella* is a major cause of diarrhea also it possesses genes that cause its virulence. *Shewanella* has *in vitro* hemolytic activity in different temperature this one of its pathogenic ability in addition to possessing enzymatic activity like protease which makes it protected against the immune system. On the medical sides this bacterium can cause infection due to its marine natural habitant so it maybe come from aquatic activity by direct contact, also immuno compromised patients are more susceptible to infection and we should remember that this pathogen is one of the microorganism that listed as (nosocomial infection pathogen).

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1. Introduction

The gram negative motile rods, can move by a single polar flagellum positive with oxidase and catalase tests. Grow on different media used for enterobacteriaceae (Ribeiro, 2010) [34].



Fig 1: *Shewanella* on nutrient agar (Shamanna *et al*., 2018) [38]



Fig 2: *Shewanella* on blood agar (Janda & Abbott 2012) [17]

The *Shewanella* genus is noteworthy not only for microbiological taxonomists due to its physiology but also for ecologists because its metabolic mechanisms dramatically influence the circulation of organic and inorganic matter. *Shewanella*e, or so-called "feomycin group" bacteria, are extensively distributed in aquatic and sediment environments and also have mutualistic or symbiotic promotion effects with other bacteria. *Shewanella* has an ecological importance instead of medical importance it has avital rule by having some abilities like bioremediation and generation of bioenergy due to its metabolic mechanisms (Mukherjee *et al*., 2020) [28].

Shewanella bacteria, containing 52 type strains that are defined by the list of prokaryotic names with standing in the nomenclature, can be classified as Group II. Aquatic *Shewanella* can also adapt to various environmental conditions and have physiologically diverse abilities; for example, they show various reduction abilities of metals, color, gas, and amide and produce lipase, protease, deoxyribonuclease, etc. However, some *Shewanella* species also reside in the human gut and generally do not cause clinical infections unless the individual involved is immunocompromised and susceptible (Yu *et al*., 2022, Li *et al*., 2024, Li *et al*.,2024) [47, 21, 22].

Study made during the period 2010-2020 showed that shewanwlla had special resistance pattern against Carbapenem antibiotics and the high percentage of its infection associated with patients has different type of systemic diseases especially related to the liver and tumors (Mukherjee *et al*., 2020) [28].

In the pursuit of continuing investigation into the relation of biofilm formation and pathogenicity for *Shewanella*, in the present study, we review genetic information dealing with *Shewanella* and also summarize biofilm-related factors which are the environment that is colonized and are known instead of target tissue. Breaking periods with *Shewanella* as an example of a sessile lifestyle in extremophiles, and especially biofilms, arguably offer valuable insights into the biology of the infection being enhanced during the continued health care of a snakebite victim or vasculitis patient. The accumulating body of evidence indicates that biofilms are intricately associated with bacterial persistence and also serve as a significant virulence factor by concealing infections during clinical obstinacy (Pugazhendhi *et al*., 2022, Dsouza *et al*., 2024, Warrier *et al*., 2021) [32, 10, 44].

2. Taxonomy and Classification of *Shewanella*

The genus *Shewanella* is composed of more than 70 species, which are Gram-negative, facultative anaerobic rods. This genus was established in 1985 because of the genetic and phenotypic characteristics that distinguish *Shewanella* from Aeromonas, Plesiomonas, and other members of the family Vibrionaceae. The classification of *Shewanella* species has undergone major changes since 1985. *Shewanella* putrefaciens was the first bacterium to be described, associated with infection in humans as of the 1920s. The comprehensive study of the phylogenetic relationships of *Shewanella* species has allowed for the stratification of the organisms into several subgroups, one of which includes mainly human pathogens. The remaining form a large phylogenetic cluster, consisting mainly of environmental organisms. (Yu *et al*., 2022, Darma *et al*. 2022, Li *et al*. 2024) [47, 9, 23]

The classification of *Shewanella* is essentially based on molecular studies, including seven housekeeping genes and three genes of the 16S-23S rRNA internally transcribed spacer region. In the large *Shewanella* cluster described from the phylogenetic point of view, there are several subclusters of high genetic diversity. One of them presents S. algae and S. upenei as the only included species, which have evolutionarily diverged from the others, representing the first branch of the *Shewanella* tree. In this sense, this study aimed to classify the species of the genus *Shewanella* while focusing on studying human pathogens through laboratory trials. In recent years, this new taxonomic status and our better knowledge of the pathogenic role of *Shewanella* in humans have pushed scientists to investigate the ability of these strains to produce biofilms. This approach appears to be fundamental to encourage future research on their potential pathogenicity and the risks involved. (Yu *et al*., 2022, Cerbino *et al*., 2023, Zhenzhou *et al*., 2023) [47, 4, 50].

3. Pathogenicity of *Shewanella*

In the genus *Shewanella*, some species are opportunistic pathogens and can cause infections in both humans and animals. Infections of susceptible individuals triggered by *Shewanella* spp. are primarily superficial and mild, but some infections can be very severe. *Shewanella* possesses several virulence factors associated with pathogenesis, such as hemolysins and proteases. The ability of *Shewanella* to form biofilms is conducive to anti-discernibility. Some *Shewanella* species can also use quorum sensing, an inter-bacterial communication system, to enhance their resistance to host defenses, while *Shewanella* putrefaciens can carry lipopolysaccharide to confuse the host immune system and establish a stable pathogen-host relationship. (Yu *et al*., 2022, Ng *et al*., 2022, Rossi *et al*. 2023) [47, 30, 35]

Hemolysins are considered not only cytotoxic factors but also harmful foundations for fish injury. These data suggest that these proteins may be critical factors of bacterial pathogenesis that ultimately lead to hemorrhagic disease. As a common exoenzyme, protease generally participates in degrading the protein components of the host immune system or extracellular matrix, leading to the enhancement of bacterial attachment ability. Many other virulence-related factors of *Shewanella* have also been detected, such as chondroitinase, staphylococcal nuclease, and extracellular collagen-like protein A; they are all reported to play certain roles in pathogenicity. The results indicate that the pathogenicity of *Shewanella* is mainly an assembly of a cascade of virulent factors. Infections caused by *Shewanella* involve infection and invading and infecting other wounds, and rarely cause bacteremia. (Wang *et al*., 2024, Kang *et al*.,

2024, Huang *et al*., 2022) [43, 18, 14].

3.1. Virulence Factors

The term "virulence factors" refers to specific elements and biochemical compounds that measure the ability of any bacterium if it can invasive the host and cause diseases (Tamez *et al*., 2021) [40].

Shewanella is not an enteric bacterium; thus, the *Shewanella*-specific factors, including adherence and invasiveness, can be established in the same manner as biofilm formation activity. In a shallow representation, adherence or colonization factors are regarded as those that prevent a bacterium from being washed off a tissue surface, invasiveness factors facilitate the invasion of host tissues, and host damage or toxigenesis factors are those for disease-inducing activity. Furthermore, the virulence factors are generally generated by a biochemical process, and it is basically the same as the internal environment a pathogen requires for its survival, whether it is settled into a host or is merely carried in the host as an incidental infection. Adherence and invasiveness factors are not always secretory proteins but can be glycoconjugates or other molecules furnished from the bacterial surface structures. Among the factors, the relationship among biofilm formation, environmental factors, and gene regulation is considered valid. The same situation can be supposed for adherence and invasiveness. (Musiol, 2023, Li *et al*., 2024, Zhang *et al*., 2024) [29, 21, 48].

In *Shewanella*, the related reports of these surface structures and the genes are not copious, as seen in some other bacteria. In S. oneidensis, type IV pili are involved in biofilm formation under anaerobic conditions and allow cells to swarm on a surface; the upregulatory genes imply a clockwise bistable switch from a less native state to a highly bioreactive state. S. putrefaciens, like other swarming bacteria that migrate over a surface under conditions of no aeration, is their virulence on the open wound. The extracellular mannose-sensitive hemagglutinin area mediated by type IV pili is involved in planktonic cell adherence to HeLa cells and is associated with biofilm formation (Chen *et al*., 2022, Ouyang *et al*., 2023, Dye, 2022) [2, 31, 11].

3.2. Infection Mechanisms

The mechanisms of infection have been widely studied for different bacteria, assimilated to a first contact between the microorganism and the host cells, which is usually generated through the incursion of some virulence factor in contact with the plasma membrane. Once the link is established, the following mechanism usually involves the processes of invasion, involving different processes such as endocytosis or through an activation process that directly affects the target host cells, which will then be internalized without affecting the viability of the microorganism, among others. When *Shewanella* secuts first contact with host cells, it is accompanied by evasion mechanisms needed to escape the immune response of the host. As with the other mechanisms described above, how this happens with *Shewanella* is unknown. The multi-host interaction spectrum is an example of how versatile *Shewanella* is, which can establish infections in a wide range of environments; however, all the mechanisms necessary for colonization may not be exclusive or take place in all different environments. For example, S. oneidensis survives in soil or water, but there is no evidence indicating that it can also be triggered in the colonization of these hosts. (Yu *et al*., 2022, Ng *et al*., 2022, Rajput *et al*., 2021) [47, 30, 33].

Evasion of the Immune Response Monocytes, neutrophils, natural killer lymphocytes, and T lymphocytes are the primary targets of *Shewanella*. Early in the infection, leukopenia and thrombocytopenia developed by one of the patients. As mentioned earlier, patients presenting these infections develop sepsis, and in the case of S. algae patients, it is not uncommon to develop invasive infections. In the context of SC and SA infections, it is important to consider the dynamics of biofilm formation by these microorganisms, associated with clinically relevant issues related to cardiovascular and wound infections. *Shewanella* spp. However, like other microorganisms, the ability to produce biofilm is not necessarily a virulence factor for pathogenicity classification. A wide number of microorganisms, including biofilm, were conducted critical review articles focusing on *Shewanella* spp. defined as clinical pathogens based on the association responsible for infections, signs, and symptoms in individuals with a compromised immune status (Chen *et al*., 2020, Zhao *et al*., 2024, Kim *et al*., 2023, Lin *et al*.2021) [8, 49, 20, 25].

4. Biofilm Formation in *Shewanella*

Biofilms form when microorganisms irreversibly adhere to a surface, grow under the appropriate conditions, and excrete extracellular polymeric substances (EPS) to encase the developing cell aggregates. This irreversible step can be globally considered the first step of surface colonization, in which the initial reversible attachment is conceptualized to be part of temporarily colonizing microorganisms, which will either dissociate upon copying or environmental factors or proceed to develop biofilms.

The term quorum sensing provide cell – to cell communication and this help the cell to regulate important biological activities one of them is biofilm formation as its clear the biofilm form when the cell of bacteria turned from planktonic to surface attachment cells. The formation of the biofilm goes through the known stages:(1) initial attachments (2) formation of micro colonies, (3) maturation of biofilm and (4) detachment, this survival mechanism considered a bright face in aquatic environment from one side it provides many advantages to these microorganisms and the other side about what they can perfume to this environment as an ecological agent so can contributes in bioremediation and biofuels (Armbruster & Parsek., 2018) [1].

Within biofilms, bacteria exhibit a variety of physiological changes, including modulation of metabolism and protein production. This global change in phenotype can lead to increased tolerance to environmental stress, increased resistance to antibiotics, and often a reduced inflammatory response due to limited accessibility to invading white blood cells. Within the lungs of patients with acute infections, decreased leukocyte chemotactic properties are often noticed for excess mucus, particularly in cystic fibrosis sufferers. Therefore, the biofilm is often the root cause of chronic infections. The natural lifestyle of bacteria is in biofilms that have, in part, been established to confer two advantages: power in numbers and a structural scaffolding to procure nutrients. Given its prevalence, biofilms should play a key role in natural environments. In the aquatic environment, microbes predominantly attach to surfaces, resulting in a distinctive population of exopolysaccharides (EPS), bacteria, and protists, known as the epiphyton, colonizing the surfaces of plants and algae. Bacteria residing in the rhizosphere of

plants are found in vast numbers and often exceed those present in the surrounding bulk water. Given that *Shewanella* species colonize surfaces, biofilms are likely to play an essential part in the function of these organisms in various biogeochemical processes, and therapies to combat infections using this genus might circumvent antibiotic-resistant biofilm infections in the future. (Muhammad *et al*. 2020, Tong *et al*. 2021, Cheah & Chan, 2021, Sauer *et al*. 2022) [27, 42, 5, 36].

4.1. Importance of Biofilms

Bacterial biofilms are the preferred lifestyle of many bacterial species, including *Shewanella* bacteria. This layer functions as a shield against environmental stress. Many sessile bacteria exhibit higher resistance to antibiotics than their free-living counterparts-in some cases, up to 1000-fold higher. Nutrients and other matter can move into the biofilm layer and nanocytic network. This can give bacteria that live within biofilms, like members of the genus *Shewanella*, more reliable access to a steady supply of certain types of nutrition than their planktonic counterparts. In general, a diverse group of microorganisms can be found in any given natural setting, and biofilms are no exception. The matrix can attract a wide variety of planktonic bacterial strains, both non-pathogenic and potentially infectious. When attempting to treat an infection, it is important to remember that biofilms can host non-pathogenic strains as well as potentially pathogenic ones. Biofilms are typically associated with chronic infections. Chronic infections are typically long-term infections that may persist in the host for years, perhaps even for an indefinite period. Chronic infections are particularly dangerous due to their strong resistance to most antibiotics. In most cases, the bacteria present within a biofilm are 1000 times more resistant to antibiotic treatment than planktonic bacteria. In addition to serving as a basis for rod and seed release, biofilms are very complicated. Physiological variations may alter the properties of bacteria within the biofilm. A mature biofilm will contain a wide range of bacterial morphologies that have adjusted to both the micro and macro environments within the biofilm. (Hu *et al*. 2021, Mukherjee *et al*., 2020, Martín-Rodríguez *et al*., 2022, Kees *et al*. 2021) [13, 28, 26, 19].

4.2. Biofilm Formation Mechanisms

Since adherence to biotic or abiotic surfaces is the initial step for biofilm formation, and in most cases the laboratory-based biofilms and naturally occurring biofilms share a lot of similarities, the attachment mechanisms between surfaces were similar to each other. In S. oneidensis MR-1, the synthesis and secretion of Flp pili could increase the attachment strength of binding substrates. The monolayer or single cell is attached to the surface by appendages and biomolecules of bacteria, and then the cells are aggregated to form a microcolony with or without flagella. The microcolony is subsequently encased into a three-dimensional community by extracellular polymeric substances, which are mainly made up of proteins, polysaccharides, lipids, and DNA, among bacteria and other microorganisms or the surface they attach. The entire process seems like a chemical reaction cascading where cell–cell and cell–surface interactions forming dense clusters contained in a hydrated matrix begin immediately after initial attachment, and microorganisms then develop protected subpopulations as biofilm. (Whitfield & Brun, 2024, Isaac *et al*., 2021, Blanco-Romero *et al*. 2024) [45, 15, 3].

In general, environmental factors, pathogenic and non-pathogenic bacteria are mainly regulated through signaling molecules and the corresponding signaling pathways, and a variety of genetic and biochemical factors including the chemotaxis receptors, sensor kinases, response regulators, and cyclic-di-GMP have indeed taken part in the biofilm formation of *Shewanella* spp., and research has also shown the different lifestyles of biofilm formation in *Shewanella* spp. under various environmental cues. Overall, the mechanism of biofilm development is complex, involving several regulators and stages. At present, the deep understanding of the mechanisms is still limited. Rather than being a recent discovery, it seems like the *Shewanella* biofilm is a higher-level cellular complexity by which its members evolved in concert with various biochemical and genetic constituents throughout their evolutionary past, and biofilms are not only a convenient lifestyle but also a clever survival mode. (Mukherjee *et al*., 2020, Yu *et al*., 2022) [28, 47].

5. Interplay between Pathogenicity and Biofilm Formation

The ability to produce biofilms, which are a favorable niche that not only protects the individual cells but also enhances the pathogenic potential of the bacterium present inside, is now a key aspect of understanding any bacterial pathogen. The rapid adaptation of a colonizer to a pathogen is usually due to biofilm production because the biofilm is difficult for the host to eradicate using natural immunity mechanisms. Our genome-wide pathogenicity profiles suggest a direct correlation of biofilm formation and pathogenicity, and indicate that during infection, the bacterium can take on dual roles: 1. as an acute attack using mobile, potential T3SS+ and biofilm-embedded cells, 2. as chronic colonizers applying biofilms. Homo-cellular adhesion is most likely to trigger pathogenicity, and because of the clear phenotypic correlated pattern, we assume that biofilm formation and pathogenicity are intricately interlinked (Pugazhendhi *et al*., 2022, Dsouza *et al*., 2024, Jahan *et al*. 2022) [32, 10, 16].

Histopathology and bioluminescence studies revealed that selected strains have the potential to form biofilms and exhibit pathogenic expressions under particular *in vivo* conditions, especially in the case of one strain owing to its more extensive survival in the host system. One noteworthy finding is that all the strains formed biofilm on a CVC, suggesting a dual role of film in the bacterial pathogen: protecting the cell and allowing them to express their pathogenicity. Extracellular polymeric substances in biofilms help to reserve necessary nutrients and other essential molecules (Schulze *et al*., 2021, Bhardwaj *et al*. 2021, Lianou *et al*., 2020) [37, 2, 24]. It has been shown that the iron in the food or host systems somehow manages to reach and come into contact with the strains in the skin or even the intestine, allowing the strains to survive and synthesize curli protein for enhanced survival on the skin or in the intestine. In an ongoing infection inside the host, the secretion systems also secrete proteases, endonucleases, and proteins to get energy-rich molecules from host systems. The bacterium can spread and successfully form a compact dual biofilm in blood culture bottles, both on the bottle wall and largely on the remarkable volume of one surviving colony (Yao *et al*. 2022, Chen *et al*. 2024, Toc *et al*.2022) [46, 6, 41]. Overall, these results suggest that biofilm formation is necessary to establish a novel human pathogenic characteristic. Establishment of a new pathogen might, in turn, be related to establishment for a new host, possibly the vertebrate evolution from fish to human. The capacity to biofilm and its relationship with colonization is a

beautifully new paradigm of research and a bridge between old and new science, with a direct link established between pathogenicity profiling and biofilm formation status of all bacteria. (Gedefie *et al*. 2021, Schulze *et al*., 2021, Silva *et al*. 2021)[12, 37, 39].

6. Conclusion and Future Directions

In this research, we analyzed the potential pathogenicity of *Shewanella* strains and their relationship with biofilm formation. Our results confirm that clinical *Shewanella* strains isolated from blood or wounds do not adhere to or form biofilms on polystyrene plates. However, they have been found to produce a weak biofilm on titanium. The classification of the species is non-pathogenic/possible pathogenic according to the proposed classification. The estimation of the risk that patients would face when acquiring a *Shewanella* infection is scarcely analyzed. The fact that some species in this genus exhibit some degree of pathogenicity leads us to the necessity to establish the degree of adherence and biofilm formation, for example, among the strains infecting immuno compromised patients or healthy individuals through water or food consumption, as well as the presence of virulence factor-encoding genes among the strains. Analyzing these infective aspects of this genus is also crucial to provide healthcare authorities with the establishment of water disinfection protocols.

In conclusion, the results obtained in this work evidenced that not all classified *Shewanella* species have conserved in their genome some genes that encode a mechanism of adhesion to surfaces in order to persist in ecosystems as microbial biofilms, but all have genes established to be crucial in this microbial strategy. Hence, there is a strong impairment concerning the relationships with the pathogens belonging to this genus, and whether they use biofilm formation as a virulence strategy or not. We believe that future lines of work within the genus *Shewanella* should include the study of the gene expression of planktonic and sessile cells and the study of quorum sensing, which would provide a better knowledge of biological processes related to many fundamental aspects of the ecological roles of *Shewanella* in a wide diversity of ecosystems.

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