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Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

Correspondence to: Muhammad Imran Qadir, miranqadir@hotmail.com

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The Bacterial Biofilm: Composition and Its Role in Infectious Diseases

Muhammad Imran Qadir and Asma Noor

ABSTRACT

A bacterial biofilm is responsible for sticking to surfaces and is embedded in a self-produced extracellular matrix of polymeric substances. Biofilms can develop on diverse surfaces, biotic, including human tissues, and abiotic, such as medical devices or industrial pipes. Bacterial biofilm structure comprises enzymes, proteins, lipids, extracellular DNA, and water. The biofilm structure of bacteria shows resistance to antibiotics and sometimes causes severe infections, mainly due to extracellular DNA. Even their mode of dispersal also provides great benefits to their survival. Their complex structure also plays an important role in their survival in natural and infectious environments.

Keywords: Bacterial biofilm, Extracellular DNA, Antibiotic resistance, Medical device infections, Cystic fibrosis pneumonia

Introduction

In nature, microorganisms are not present as dispersed single cells; they are compiled at surfaces as aggregates or congeries of poly-microbial sludge, tangles, or mats. In bacterial biofilm, the extracellular material, for example, the matrix, accounts for 90%, and only 10% of the dry mass is present. The biofilm cells are engrafted in a structure known as extracellular polymer substances (EPS).^{1,2} This provides great benefit against several antibiotics for the survival of bacterial biofilm. All elements, such as DNA, a genetic material of lysed cells, lipids, and nucleic acid, are present in the matrix. The presence of microorganisms in biofilm also affects the composition of EPS. However, Gram-negative bacteria have a wide range of DNA and enzymes, so sometimes they act as a competing structure of biofilm. In prehistoric times, biofilm formed in old fossils that are 3.4–3.5 billion years.³ So it also shows that prokaryotes also characterize biofilm formation.⁴ In the evolution of eukaryotes from prokaryotes, the biofilm structure also shows resistance to harsh temperatures and other environmental conditions because it can change its structure with the availability of nutrients.^{5,6} The leaning ability of bacteria in a vast environment is undoubtedly connected with the changing surface of the Earth and the ecosystem.

Components of Biofilm

The morphology diversity of bacterial biofilm and its importance in all types of environments have significantly increased over the past 10 years. The experimental observation for biofilm structure reveals that sessile or stalk-less bacteria colonies have heterogeneous matrix-enveloped microcolonies, so this shows that biofilm structure is not simple.⁷ The power of channels in facilitating nutrient intake, with the help of infusing liquids into biofilm and waste material

exchange, gives strong associations between many functions.⁸ The structure of biofilm also depends on the availability of nutrients, ranging from a flat shape to a mushroom-like body.

Enzymes

A diverse range of extracellular enzymes is present in biofilm, which are helpful for synthetic and biopolymer degradation, such as plastic, or by attacking the backbone of polymers.⁹ Microbial molded corrosion also occurs through extracellular redox enzymes.¹⁰ The presence of enzymes involved in the degradation of EPS components changes them into low molecular weight compounds, and these products are used as a source of carbon or energy. Breakup of bacteria from the biofilm also occurs if enzymes degrade the EPS structure. Extracellular enzymes are also efficiently maintained in the biofilm matrix by interacting with polysaccharides.¹¹ The association of extracellular lipase with alginate forms by *Pseudomonas aeruginosa* is founded on fragile binding forces, so this hypothesis supports the molecular modeling.¹² This type of arrangement also retains enzymatic activity close enough to the cell to keep the diffusion lengths of enzymatic products shorter and also optimizes their intake by bacteria.¹³ Moreover, the thermo stability relationship for enzymes also rises.

Extracellular DNA

Various origins of biofilm have enclosed DNA,¹² but it is accounted to be present in especially large amounts in wastewater biofilm, though the amount can vary between closely related species.¹⁴ It is also a structural component in the biofilm matrix of *Staphylococcus aureus*.¹² Though eDNA was first observed as residual material of lysed cells. EPS consists of carbohydrates, protein, and nucleic acids. eDNA was localized widely in all biofilms.^{15,16} However, localization differs between different structures, like in flat or mushroom-like bodies.

Lipids

The biofilm matrix also contains lipids.¹⁷ Lipopolysaccharides are important for the attachment of lipids to the surfaces of many materials.¹⁸ Many surface-active EPS, such as surfactin, viscosin, and emulsan, can disseminate hydrophobic material and make it bioavailable.¹⁹ They are also useful for microbial enhanced oil production and bioremediation of oil spills.²⁰

Bio-Surfactants

They have antibacterial and antifungal attributes and also prevent bacterial attachment.¹⁹ Bio-surfactants produced by microorganisms at the surface of the

air–water interface have an important function, like surface tension and gas exchange between oceans and atmosphere.²⁰ They depict surface action and increasing surface-related bacterial motility and establishment of mushroom-like anatomical structures, forbidding the settlement of canalizers, so they play an essential part in biofilm diffusion.

Water

Water is present in a large proportion of biofilm. The matrix of EPS contains extremely hydrated surroundings, so it dehydrates less than its environment.²¹ In the varying temperatures, it acts as a buffer to protect the biofilm from desiccation.²² The structure of EPS is hygroscopic, so the mechanism of water binding is less efficient. In the presence of excess water, hydraulic decoupling occurs to protect bacteria from saturated soil.^{23,24} During desiccation, the concentration of EPS causes an increase in count in nonspecific binding sites so that they can react among themselves, and the volume of bacterial biofilm also reduces.²² EPS matrices also have a polar, anionic, and cationic region. So the presence of water provides great protection during harsh environmental conditions.

Dispersal of Bacterial Biofilm

Three discrete biofilm dissemination Schemes can be viewed in Table 1.

Infections Caused by Bacterial Biofilm Infections Associated with Devices

Although endovenous catheters, prosthetic heart and joint devices, and artificial pacemakers for the heart play a vital role in saving lives, they are also associated with several infections. Risks associated with these devices were first observed in the 1980s when scientists first noted the disease-causing bacteria on the surface of certain medical instruments. *Staphylococci* are the microorganisms mostly associated with certain medical devices used to treat various diseases, such as

chemotherapy or invasive medical treatments.³¹ Formation of bacterial biofilm also leads to new infectious diseases, like invasive infection associated with polymer.³² So, bacterial biofilm formation is considered a factor of virulence, a bacterial factor that leads to infection. The most important feature for the pathogen *Staphylococcus* attachment on medical devices is its enormous number of EPS, which protects it from the natural defense mechanisms of the host body and antibiotics. Biofilm formation occurs through two basic levels in *Staphylococci*: Attachment of bacteria to the solid surface, accompanied by growth-dependent aggregation of cells, which causes multiple strata for cell clusters.³³ The arrangement of cell layers in *S. epidermidis* has been recognized as a cell-cell adhesion mechanism, associated with 1,6-related glycosaminoglycan, also known as intercellular polysaccharide adhesion. The Protein involved in forming the matrix of polysaccharides is regulated in *S. epidermidis* by the gene locus. This locus is also conserved in many phylogenetically related species of *Staphylococci*. If a mutation occurs in this gene locus, it also disturbs the bacterial biofilm formation and accumulation. The biofilm formation also becomes unsuccessful if there is an abnormality in the original adherence. Hydrophobicity and electrostatic burden on the medicinal material can also manipulate the association between surface and chemical compounds on the bacterial cell. The surface of bacterial protein plays an important role in sticking to the host and forming biofilm in *Staphylococcus* species. The attachment of *S. epidermidis* to the polystyrene is also mediated by AtlE, a protein having the ability to bind to the extracellular matrix of the host known as Vitronectin. The biofilm formation in *S. epidermidis* is also enhanced by Mg²⁺ and inhibited by EDTA.³⁴ Some other proteins, like biofilm-associated protein or accumulation-associated protein, play a vital role in the formation of bacterial biofilm. The host body can also behave differently in infections related to the device, especially with *staphylococci*. Several receptors on the surface of a cell known as adhesions also bind with the molecules of a host, such as protein or glycoprotein. Most of these proteins are associated with microbial components that can bind to adhesive molecules of the matrix; they interfere with binding to several types of host cells and also with the plasma proteins of the host.³ Thus certain species of bacteria can utilize the host metabolic machinery that are formed in healing of wounds, it also indicates the binding of bacteria also supplies it with an alternate mechanism in which the migration of host occur on living but also on the surface of devices which are used for therapeutic purposes (Figure 1).

Inflammation of the Endocardium and Heart Valves

Bacterial biofilm matrix is also related to bacterial origin, though this term is used mostly for biofilms developed on laboratory abiotic surfaces. However, the infections caused by bacterial biofilm on the tissues or cells of the host are also components of infections associated with the surface. A remarkable example is

Table 1 | Biofilm dissemination schemes

Swarming or Seeding Dispersal	Dispersal by Clumping	Dispersal by Surface
This mode of dispersal is best for non-mucoid bacterial biofilm structures. They form a stationary extracellular structure. ²⁵ However, the intracellular micro colony region allows the moving cells to move outside by making holes. ²⁶	The entire aggregate can be removed from the bacterial biofilm in this dispersal mode. This aggregate contains cells bordered with EPS. ²⁷	This mode of dispersal occurs through motility by gliding or through shear-mediated channels. It can also be considered as a result of medication and reported also in the lungs of certain patients as a result of tubes or catheters inserted in pneumonia patients. ^{28,29}
Liquefaction can be assigned as the lysed population or third physical composition of the bacterial population due to the death of cells, and the remaining cells are considered negative. ²⁶ The lysing population can be regarded as a third phenotype, whereas the remaining swarming cells are characterized by negative tenacity.	Their dispersal is thought to be fluid, similar to wind dispersal. However, their dispersal is not controlled. They can also shed clumps of cells that contain human pathogens. Some of these clumps have enough resistance against antibiotics, and their resistance is similar to swarming dispersal.	However, this mode of dispersal is more resistant because it is more resistant to certain antibiotics. ³⁰

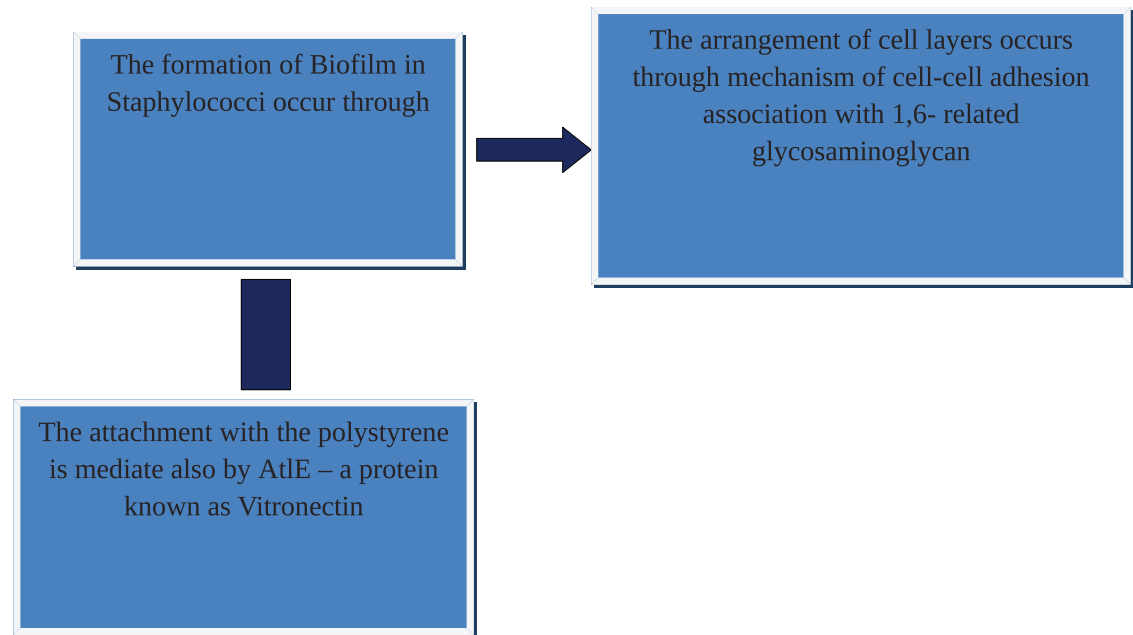


Fig 1 | Bacterial biofilm: an overview

endocarditis caused by bacteria.³⁵ Streptococci cause most endocarditis infections; most strains are found on oral and skin surfaces. The wounds caused by bacterial endocarditis consist of bacterial cell aggregates, fibrin, and platelets devoted to damaging the cardiac valve epithelium. It is also linked with inborn heart defects, prosthetic valves of the heart, and vascularity in grafts. It is most likely caused by clots formed by platelets or fibrin, which accumulate at turbulent flow provoked by tissue abnormalities, heart disease, or an existing vascular catheter. The basic basement membrane exposed by damaged endothelium is composed of laminin, collagen, fibronectin, and Vitronectin; thus, it supports the attachment of bacteria. Numerous studies show that the binding ability of bacteria with the surfaces of tissues sets up a restricted site for infection caused by the interaction of bacterial attachment and the tissues of the host. Ramirez-Rhonda studied the ability of streptococcal species to bind with the cardiac valves and observed that EPS consists of glucans, and dextrans attach better to the damaged heart valves. *Streptococcus parasanguis*, a colonist of the surface of human teeth and an inhabitant established in native, prosthetic heart valves, encodes a gene, *Peritrichous fimbriae*, *fap1*, which is linked with the formation of biofilm on the surface of plastic. A mutant *fap1* shows limited attachment, but mainly fails to accumulate and form microcolonies. The turbulent flow of bacterial endocarditis also contributes to the establishment of vegetation. Though turbulency was conventionally considered to induce the formation of clots and damage to tissues, it is believable that bacterial biofilm clump cells react to the flow of turbulency by producing EPS. Significantly, antibiotic therapy for the cure of endocarditis depends on the biofilm. In a rabbit model infected with the infectious agent *E. coli*, it required continuous concentration of antibiotics, and it was

220 times the blood serum, which has a bactericidal concentration. Still, if the vegetation was treated with ex vivo antibiotics, the antibacterial activity required 150 times less bacterial concentration.

Cystic Fibrosis Pneumonia

It is a recessive autosomal disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which results in dysfunctional electrolyte discharge and absorption. The reductions in hydration of the surface of airway fluid give more viscosity to the respiratory mucus and also contribute to cystic fibrosis (CF). Pulmonary infection of the lower respiratory tract of patients with CF starts in immaturity or early infancy, caused mostly by *Staphylococcus aureus* or *Haemophilus influenzae*. However, in teenage years and childhood, most patients of CF become infected with *P. aeruginosa*. The transition from migration of new bacteria to invasive infection by *P. aeruginosa* appears to stem from the atypical environment of the cystic fibrosis lung, which enables asialylated receptors on epithelial cell surfaces to promote *P. aeruginosa* attachment, thereby hindering mucociliary clearance. Another speculated mechanism of colonization of bacteria in CF implies the layer of mucous membrane. In this example, the increase in viscosity of the CF. Airway mucus also behaves as a matrix for support. Recent studies on patients of CF having chronic disease of lungs by the use of electron microscope show that *P. aeruginosa* is present in Mucous hypoxia of 100 µm diameter in the lumen of the airway instead of being attached to the epithelium.

Experiments showed that oxygen is also exhausted in these mucoid macro colonies. In the multifarious environment of CF lung, it is unconvincing that there is a special means of pathology, so the host's inflammatory response. It also brings change of the limited

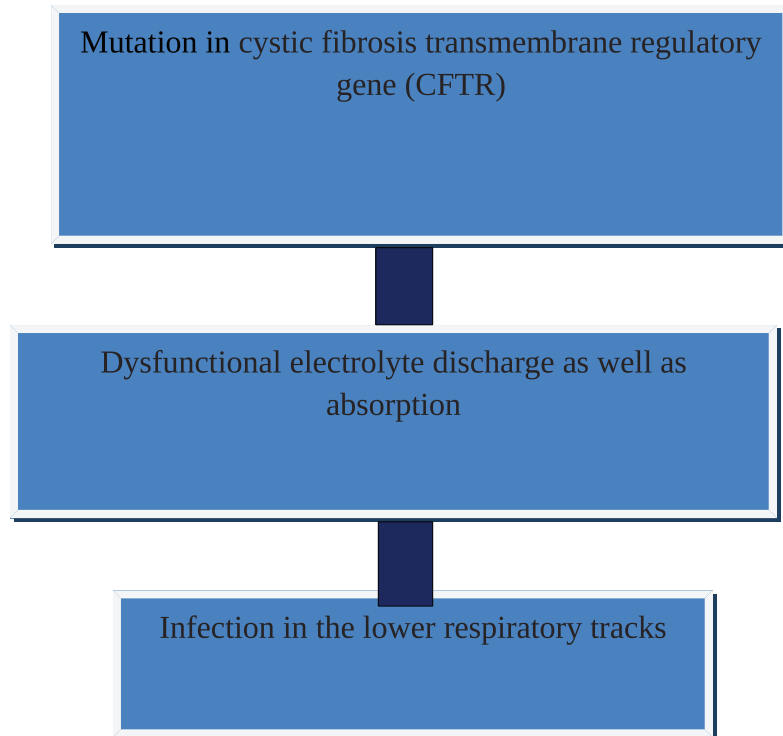


Fig 2 | Cystic fibrosis pneumonia

microenvironment in which *P. aeruginosa* respond. So, it is cleared that in CF pneumonia, the compound relations among bacteria and restricted environmental remain host having the inflammatory response leads to the pathology of complex diseases (Figure 2).

Biofilm Implications in Resource-Limited Settings

Biofilms are clusters of bacteria or other microorganisms that adhere to surfaces and form a protective, sticky layer. In resource-limited settings, biofilms present a significant challenge due to their resistance to antibiotics, immune responses, and cleaning methods. These challenges can amplify existing healthcare issues. Here are some key implications of biofilm formation in such environments:

1. Increased infection rates and chronic infections
2. Antibiotic Resistance
3. Limited diagnostic and treatment options
4. Poor infection control

The presence and persistence of biofilms in resource-limited settings exacerbate existing public health challenges, leading to chronic infections, increased treatment costs, and higher mortality. Addressing these issues requires targeted interventions that improve diagnosis, prevention, and treatment while considering the unique limitations of these environments.

Current Status

Biofilm research has made significant advances in our understanding of the complex structures and behaviors of microbial communities that adhere to surfaces.

Recent studies have explored the genetic expression of biofilm-associated organisms, revealing how these communities adapt to extreme environmental conditions, such as high temperatures, extreme pH, and hypersalinity, thus providing bacteria with evolutionary advantages.³⁶

A major focus has been combating the enhanced antibiotic resistance exhibited by bacteria within biofilms. These biofilms can exhibit a 10–1000-fold increase in antibiotic resistance compared to similar bacteria living in a planktonic state.

Researchers are exploring various strategies, including targeting EPS, dispersal molecules, quorum sensing, and dormant cells, to disrupt biofilm formation and persistence.³⁷

Advancements in technology have facilitated the development of microfluidic bioanalytical flow cells, enabling real-time, non-destructive monitoring of biofilm formation and response to antibiotics. This approach provides deeper insights into the antimicrobial resistance (AMR) mechanisms of biofilms. Moreover, the design of porous metamaterials using Bayesian learning has been proposed to control biofilm transport properties, offering potential applications in pollution reduction, material self-healing, and energy production.³⁸

These collective efforts enhance our understanding of biofilm biology and create new strategies to prevent and treat biofilm-related infections and industrial fouling.

Future Consideration

Future considerations for biofilm research are focused on understanding its complex structure and behavior in diverse environments, including natural ecosystems and medical settings. Advancements in technology, such as imaging techniques and molecular analysis, are expected to provide deeper insights into biofilm formation, maintenance, and resistance mechanisms. Addressing biofilm-related challenges, particularly concerning antibiotic resistance, will be critical for developing new treatment strategies for chronic infections and industrial contamination. Furthermore, exploring biofilms' potential in bioremediation, wastewater treatment, and bioengineering could lead to innovative applications. Integrating synthetic biology and biofilm engineering holds promise for creating functional biofilms tailored to specific needs, enhancing their role in environmental sustainability and biotechnology.

Clinical and Technological Challenges of Biofilm

Many clinical and technological challenges are faced, making them difficult to manage and treat effectively. From antibiotic resistance and chronic infections to technological limitations in detection and treatment, biofilms present an ongoing challenge to healthcare professionals and researchers. Innovations in diagnostic technologies, antimicrobial therapies, and device design are needed to better address these challenges and improve patient outcomes. Until then, managing biofilm-related infections will require a combination of prevention, early detection, and the development of new, targeted therapies.

Future Research Questions

Biofilm research is rapidly evolving, presenting a multitude of complex questions that remain to be fully answered. Future research studies will likely focus on understanding the molecular and environmental factors that drive biofilm formation, developing innovative detection and treatment strategies, and addressing the global challenges posed by antibiotic resistance.

Some of the examples of future research questions for biofilm may be:

- How do different environmental factors influence biofilm formation?
- What is the role of the extracellular matrix in biofilm stability?
- How do biofilms contribute to AMR?
- How do biofilms interact with the host immune system?
- What are the ethical and societal implications of new biofilm-targeting technologies?

Conclusion

The microbiology of bacterial biofilm is complex. The presence of EPS in bacterial biofilm leads to infections, which may be lethal.

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