Review Article

Perspectives on Biofilm Challenges and Solutions

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ABSTRACT

Biofilms consist of an extracellular polymeric matrix that protects microorganisms from external stresses, such as antibiotics and the host immune response, making microbial infections difficult to treat. Biofilm-associated infections are on the rise, often leading to chronic conditions and resistance to multiple drugs, resulting in increased mortality rates. This necessitates special consideration when selecting materials for implants, lenses, sutures, prosthetics, and other medical devices. In this review, we discuss various approaches for biofilm inhibition, their mechanisms of action, and the challenges associated with their clinical translation.

Keywords: Antibiofilm agents, bacterial infection, biofilm, drug resistance, implants

Biofilms are formed when microorganisms adhere to one another and solid surfaces. These attached cells get embedded in a matrix made up of extracellular polymeric substances, creating a thin film that provides a protected environment for the microorganisms.[1-3] Approximately 80% of infections are associated with biofilm formation,[4] which is commonly found on medical devices[5] such as knee replacements, catheters, implants, prosthetic valves, contact lenses, screws, pins, and joints. This biofilm formation significantly affects antimicrobial efficacy and immune responses,[6] contributing substantially to antimicrobial resistance[7,8] and presenting serious healthcare challenges. To address this issue, various strategies have been implemented, including the use of antimicrobial peptides,[9-11] modifications to medical devices,[12,13] quaternary ammonium compounds,[14-16] compounds that release nitric oxide,[17,18] inhibitors of cell signaling pathways,[19-22] antibiotic conjugates,[23-25] photothermal therapy (PTT),[26] and surgical removal of biofilm biomass.[27]

Antimicrobial peptides, composed of 10–50 amino acids, exhibit potent antimicrobial and antibiofilm activity. Their antimicrobial mechanism involves permeating cell membranes, leading to the formation of membrane-spanning pores. This destabilizes the membrane and neutralizes or disaggregates lipopolysaccharides. However, their antibiofilm activity is attributed to their ability to disrupt cell membranes and interfere with quorum sensing, thereby inhibiting the adhesion of bacterial cells to solid surfaces.

Another promising strategy for preventing microbial biofilm formation on invasive medical devices involves modifying their surfaces using biocides or developing anti-adhesive materials. However, there is ongoing debate regarding biocide coatings, particularly concerning the potential development of antibiotic resistance due to long-term use and the release of sub-inhibitory drug concentrations.

Quaternary ammonium salts (QAS) have also been proven to demonstrate antibiofilm activity by penetrating the cell wall and interacting with lipids and proteins in the cell membrane, leading to structural

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disorganization and ultimately causing cell lysis. The activity and selectivity of QAS depend on their chain length, charge, and monomeric or dimeric nature.

An alternative strategy for biofilm disruption is the use of exogenous nitric oxide (NO)-releasing agents. This approach presents a promising option due to its ability to disperse and inhibit biofilms. NO donors, including small molecules, macromolecules, and nanoparticles, can be utilized to generate highly reactive NO, which interacts with oxygen, transition metals, DNA, and proteins, resulting in potent antibiofilm and antimicrobial effects.

Molecular-level studies on the mechanism of biofilm formation have revealed that cyclic-di-GMP, a secondary signaling molecule, plays a crucial role in the biofilm life cycle. High levels of cyclic-di-GMP are directly linked to biofilm formation, whereas reduced levels promote biofilm dispersal. Further research has demonstrated that diguanylate cyclase (DGC) catalyzes the synthesis of cyclic-di-GMP, while phosphodiesterase (PDE) facilitates its degradation. Consequently, several DGC and PDE modulators have been identified to regulate cyclic-di-GMP levels, offering a potential strategy to control biofilm formation.

The development of resistance to conventional antibiotics is largely attributed to reduced drug permeation through the exopolymeric matrix of biofilms. To overcome this resistance mechanism, a promising approach involves the use of antibiotic conjugates, where antibiotics are linked to membrane-penetrating peptides or polymers. In addition, conjugating antibiotics with nanoparticles offers a valuable strategy for enhancing drug penetration through bacterial biofilms.

Another promising approach for combating biofilms is PTT, which offers several advantages, including its non-invasive nature, broad-spectrum activity, shorter treatment duration, and low systemic toxicity. The effectiveness of PTT depends on laser properties and the selection of suitable photothermal agents. Furthermore, PTT has shown significant potential as a combination therapy when used alongside antimicrobial agents and nanotechnology, enhancing its overall efficacy against biofilms.

Over the past decade, research has increasingly focused on designing and developing nano/micromotors (NMMs) to effectively disrupt microbial biofilms.[28-36] NMMs are notable for their ability to harness external or environmental energy and convert it into propulsion. This capability can be strategically employed for the physical and chemical disruption of biofilms. The mechanism involves the deeper penetration of NMM into the extracellular polymeric matrix by utilizing driving forces from external or internal sources, such as hydrogen peroxide, magnetic fields, or ultrasound. Although NMM appears to be a promising strategy against biofilms and addresses serious issues of drug resistance in clinical settings, there are still future challenges to consider. These challenges include large-scale production, stability, treatment efficiency, and *in vivo* translation, all of which need to be addressed in future research in this area.

Biofilms are now recognized as a critical global issue impacting the healthcare, food, water, and marine industries, resulting in significant health and economic burdens worldwide. Fundamental challenges in biofilm research include the development of *in vitro* assay protocols and computer-aided models that accurately replicate real-life environments, as well as bridging the gap between oversimplified models and the highly complex and diverse nature of biofilm development. In addition, the lack of standardized guidelines for diagnosing and categorizing biofilms, testing antibiofilm agents, and providing physicians with treatment protocols for biofilm infections continues to hinder progress in biofilm research. The development of Food and Drug Administration -approved antibiofilm drugs and the translation of nanotechnology for their successful clinical applications, particularly in chronic and multidrug-resistant biofilm infections, remain major current challenges for researchers in this field.

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