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# A Review of Antibacterial Peptides Against Bacterial Biofilms

Bacterial biofilms are structured microbial communities formed when bacteria adhere to biological or non-biological surfaces and become enveloped by extracellular polymers secreted by themselves. This state enhances bacterial resistance to antibiotics and host immune systems by 10 to 1000 times, making it a primary cause of chronic infections, healthcare-associated infections, and treatment failures. Traditional antibiotics are effective against planktonic bacteria but struggle to penetrate and eradicate biofilms. Antimicrobial peptides, a class of small-molecule peptides widely present in the innate defense systems of organisms, are considered a highly promising new strategy for combating biofilm-associated infections due to their unique mode of action. This review summarizes the mechanisms of action, application advantages, and current challenges of antimicrobial peptides against bacterial biofilms.

## I. Formation of Bacterial Biofilms and Therapeutic Challenges

The formation of biofilms is a dynamic process primarily comprising four stages: reversible/irreversible attachment, microcolony formation,

maturation, and dispersion. Mature biofilms exhibit a highly structured three-dimensional architecture, with their core composed of an extracellular polymeric matrix secreted by bacteria. Key components include polysaccharides, proteins, nucleic acids, and lipids. This matrix forms multiple barriers:

Physical barrier: Impedes the penetration of most antibiotic molecules.

Chemical barrier: Its anionic components adsorb and neutralize positively charged antibiotics.

Physiological barrier: Internal bacteria exhibit low metabolic activity, existing in a “dormant” state, rendering them insensitive to antibiotics targeting active metabolic processes.

Genetic barrier: Facilitates gene transfer at the genetic level, accelerating the spread of resistance genes.

These characteristics render traditional antibiotic therapies largely ineffective against biofilm infections, creating an urgent need to develop novel anti-infective agents that target the unique biological properties of biofilms.

## II. Mechanism of Action of Antibacterial Peptides Against Biofilms

Antimicrobial peptides combat biofilms not through a single mechanism, but by inhibiting formation and promoting clearance through synergistic actions targeting multiple pathways and stages.

### 1. Inhibiting Biofilm Formation and Early Intervention

During the initial stages of biofilm formation, antimicrobial peptides can intervene through the following mechanisms:

Inhibiting bacterial adhesion: Many antimicrobial peptides can competitively bind to surfaces—such as materials or host cells—via electrostatic or hydrophobic interactions, forming a "fouling-resistant coating" that blocks initial bacterial attachment.

Disrupting quorum sensing: Quorum sensing is the chemical signaling system through which bacteria communicate and coordinate collective behavior, including biofilm formation. Certain antimicrobial peptides mimic or interfere with these signaling molecules, blocking signal transduction pathways and inhibiting the transition from planktonic to biofilm states.

2. Penetrating and Disrupting Mature Biofilm Structures

This represents one of the core advantages distinguishing antimicrobial peptides from traditional antibiotics.

Penetrating Matrix Barriers: Most antimicrobial peptides carry positive charges, enabling them to interact with negatively charged extracellular matrix components. This allows effective penetration through dense matrix layers to reach deep-seated bacterial cells.

Dissolving Matrix Components: Some antimicrobial peptides possess the ability to degrade or depolymerize key matrix components. For example, peptides with nuclease activity can degrade extracellular DNA,

which serves as a crucial “scaffold” for biofilm structural stability and adhesion. Other peptides may disrupt the physical integrity of the matrix by destroying protein-protein interactions or hydrolyzing polysaccharides.

3. Eradicating Bacteria Within Biofilms

Upon entering biofilm interiors, antimicrobial peptides directly eliminate bacteria through primary mechanisms:

Membrane Damage Mechanism: This is the classic pathway. Positively charged peptides interact electrostatically with negatively charged bacterial membranes, disrupting integrity via mechanisms like the “barrel-plug model” or “carpet model.” This leads to leakage of cellular contents and cell death. This physical disruption is rapid and less likely to induce traditional bacterial resistance.

Intracellular Targeting Mechanism: Some antimicrobial peptides can penetrate the cell membrane without immediate lysis, subsequently binding to intracellular targets. This inhibits nucleic acid or protein synthesis, or enzyme activity, leading to bacterial death.

4. Inducing biofilm dispersion

Certain antimicrobial peptides can “awaken” or stimulate bacteria within biofilms, causing them to revert from a stable biofilm state to a free-floating state. While this dispersion may temporarily increase local bacterial counts, it re-exposes bacteria to antibiotics and immune system attacks, creating conditions for combined therapies.

## III. Optimization Strategies for Antibacterial Peptides Targeting Biofilm Treatment

To enhance the anti-biofilm efficacy of antimicrobial peptides, researchers have developed multiple design and delivery strategies:

### 1. Peptide Molecular Structure Optimization

Enhancing membrane activity and permeability: By rationally designing amphiphilic structures, optimizing net positive charge density and hydrophobicity, a balance is achieved between bactericidal activity and the ability to penetrate biofilm matrices.

Enhancing stability: Incorporating D-amino acids, cyclization, or terminal modifications to resist protease degradation within biofilm microenvironments.

Functional fusion design: Constructing multifunctional fusion peptides. For example, linking membrane-active antibacterial domains with domains that specifically bind matrix components to achieve targeted enrichment in biofilms; or fusing antimicrobial peptides with quorum sensing inhibitor peptides to simultaneously inhibit biofilm formation and exert bactericidal effects.

### 2. Combined Therapy Strategies

Combining antimicrobial peptides with traditional antibiotics, biocides, or physical methods is an effective approach to enhance efficacy and reduce resistance.

Combination with Antibiotics: Antimicrobial peptides disrupt biofilm structure and damage bacterial membranes, significantly enhancing antibiotic penetration and uptake. This produces synergistic bactericidal effects and effectively targets dormant bacteria.

Combination with Chelating Agents (e.g., EDTA): Chelating agents destabilize the biofilm matrix. When combined with antimicrobial peptides, they enhance penetration and bactericidal efficacy.

3. Advanced Delivery Systems

Integrating peptides into delivery systems is a key strategy for protecting them and achieving sustained local release.

Hydrogels: Hydrogels loaded with antimicrobial peptides can serve as wound dressings, continuously releasing high-concentration peptides at infection sites while maintaining a moist environment.

Nanoparticles/Coatings: Antimicrobial peptides can be immobilized on medical device surfaces to form anti-biofilm coatings or encapsulated within nanoparticles for targeted delivery to infection sites.

IV. Challenges and Future Outlook

Despite promising prospects, antimicrobial peptides face challenges in advancing toward clinical applications for biofilm treatment:

In vivo activity and stability: Complex in vivo environments (salt ion concentration, serum proteins, pH) may inhibit peptide activity; protease degradation leads to short half-lives.

Selective toxicity: Ensuring high efficacy against bacterial biofilms while minimizing toxicity to host cells requires meticulous design.

Production Costs: Large-scale synthesis of high-purity, modified peptides incurs significant expenses.

Lack of Standardized Evaluation Models: The absence of standardized models fully simulating the complex chronic biofilm infection environment in vivo compromises the accuracy of preclinical predictions.

Future developments in this field will focus on:

Rational Design and High-Throughput Screening: Combining artificial intelligence and machine learning to reverse-engineer superior peptide sequences based on biofilm characteristics.

Smart Responsive Systems: Developing peptide prodrugs or delivery systems that activate or release upon sensing specific biofilm microenvironment signals (e.g., low pH, specific enzymes).

In-Depth Mechanistic Research: Utilizing imagingomics and transcriptomics to elucidate the dynamic interactions between antimicrobial peptides and biofilm components at microscopic levels.

Exploring natural resources: Discover novel antimicrobial peptides with unique anti-biofilm activity from extremophile organisms.

## V.Conclusion

Antimicrobial peptides offer a revolutionary new approach to

eradicating stubborn bacterial biofilm infections through their multi-mechanism, multi-target action. Not only can they directly kill bacteria protected by biofilms, but they also actively disrupt the physical and biochemical barriers of biofilms, fundamentally dismantling these bacterial "fortresses." Although further optimization is needed in areas such as in vivo stability, selectivity, and production costs, the convergence of synthetic biology, nanotechnology, and artificial intelligence holds promise for advancing antimicrobial peptides from laboratory research to clinical practice. Ultimately, they are poised to become a key weapon in tackling the global challenge of drug-resistant biofilm infections, laying a solid foundation for developing next-generation anti-infective therapies.