Review

How New Peptides Combat MRSA: Mechanisms, Resistance, and Translational Challenges : A Narrative Review

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How New Peptides Combat MRSA: Mechanisms, Resistance, and Translational Challenges : A Narrative Review

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a significant global health threat due to its multidrug resistance, biofilm formation, and high virulence, which collectively limit the efficacy of conventional antibiotics and drive the need for alternative therapeutic approaches. Objectives: To review the current progress in antimicrobial peptides (AMPs) as therapeutic candidates against MRSA, focusing on mechanisms of action, resistance circumvention, formulation strategies, translational challenges, and future perspectives. Methods: Narrative review of recent studies on AMPs targeting MRSA, including peptide engineering, chemical modifications, and delivery approaches to enhance stability, potency, and specificity. Results: AMPs exert multifaceted effects such as membrane disruption, inhibition of intracellular targets, interference with biofilm formation, and modulation of host immune responses. Their pleiotropic mechanisms reduce the likelihood of resistance development, and engineering strategies including cyclization, stapling, and conjugation with lipids or nanoparticles improve pharmacokinetics and target specificity. Conclusions: AMPs represent promising therapeutic alternatives against MRSA. Understanding their mechanisms, optimizing peptide design, and developing effective delivery strategies are essential for clinical translation in the post-antibiotic era.

Keywords: MRSA; antimicrobial peptides (AMPs); biofilm; peptide engineering; translational challenges; therapeutic strategies

1. Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) continues to pose a significant threat in both healthcare and community settings. The infections caused by MRSA range from superficial skin lesions to life-threatening conditions such as bacteremia, endocarditis, pneumonia, and osteomyelitis (Lee et al., 2018; Turner et al., 2019). Globally, MRSA accounts for high morbidity and mortality rates, creating substantial healthcare costs and socio-economic burdens (Tong et al., 2015; Hassoun et al., 2017). The diminishing effectiveness of conventional antibiotics, coupled with a stagnant development pipeline, underscores the urgent need for novel therapeutic strategies (Magana et al., 2020).

Antimicrobial peptides (AMPs), small cationic molecules present in a wide range of organisms, provide a promising alternative to traditional antibiotics. Unlike antibiotics that often target a single bacterial pathway, AMPs exert multi-faceted actions, including membrane disruption, inhibition of intracellular targets, interference with biofilm formation, and modulation of host immune responses (Mahlapuu et al., 2021; da Cunha et al., 2022). This broad-spectrum activity reduces the likelihood of resistance development. Advances in peptide engineering, such as cyclization, stapling, and conjugation with lipid or nanoparticle carriers, further enhance stability, potency, and specificity (Huan et al., 2020; Zhang et al., 2021). This review synthesizes the current knowledge on MRSA-

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targeting peptides, focusing on mechanisms of action, resistance circumvention, formulation strategies, translational challenges, and future directions.

2. Mechanisms of Antimicrobial Resistance in MRSA

MRSA's remarkable resilience stems from its diverse resistance mechanisms. The acquisition of the mecA gene, encoding an altered penicillin-binding protein (PBP2a), is central to methicillin resistance, allowing cell wall synthesis in the presence of β-lactams (Hartman & Tomasz, 1984; Peacock & Paterson, 2015). Additionally, the mecC gene, detected in both clinical and zoonotic isolates, broadens the genetic basis of resistance (Shore et al., 2011). Resistance to other antibiotic classes is mediated by multiple pathways: erm genes confer MLSB resistance, aminoglycoside-modifying enzymes target aminoglycosides, tetK/tetM efflux or ribosomal protection confers tetracycline resistance, and gyrA/parC mutations reduce fluoroquinolone susceptibility (Chambers & DeLeo, 2009; Hooper, 2001).

Biofilm formation is another critical factor in MRSA pathogenicity. Within these biofilms, bacterial cells are embedded in an extracellular matrix that reduces metabolic activity, impedes antibiotic penetration, and facilitates horizontal gene transfer. This structural complexity contributes to chronic infections and heightened antimicrobial tolerance (Otto, 2013). Additionally, MRSA expresses a variety of virulence factors, including surface adhesins, α-toxin, and Panton-Valentine leukocidin (PVL), which further enhance pathogenicity and complicate treatment (Löffler & Tuchscherr, 2017). Collectively, these mechanisms—genetic resistance, biofilm formation, and virulence factor expression—underlie the limited success of conventional antibiotics and underscore the urgent need for alternative therapeutic strategies (Figure 1).

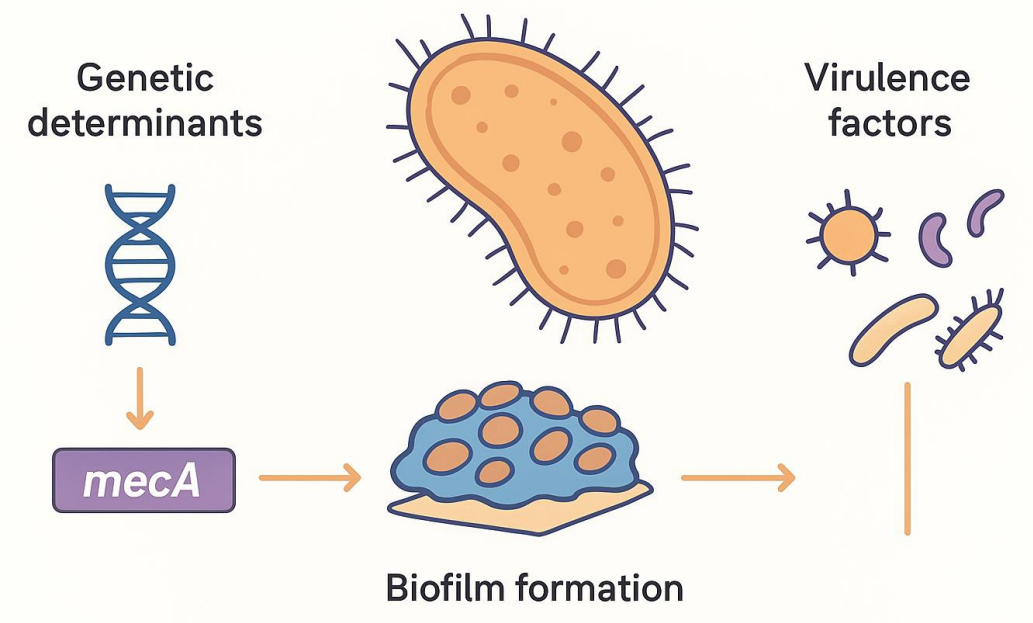

Figure 1. MRSA Resistance Mechanisms: Genetic determinants, Biofilm formation, and Virulence factors.

3. Antimicrobial Peptides as Emerging Therapeutics

AMPs are typically 10–50 amino acid residues, cationic, and amphipathic, enabling strong interactions with negatively charged bacterial membranes (Zasloff, 2002). Their primary mechanism involves membrane disruption, causing rapid bacterial death and minimizing resistance development (Hancock & Sahl, 2006). Certain AMPs penetrate bacterial cells, inhibiting DNA, RNA, or protein synthesis, while others prevent biofilm formation or disrupt established biofilms (Otto, 2013). Moreover, AMPs can modulate host immune responses, enhancing chemotaxis, promoting wound healing, and attenuating excessive inflammation (Mahlapuu et al., 2016). As illustrated in

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Figure 2, antimicrobial peptides (AMPs) are typically 10–50 amino acid residues, cationic, and amphipathic, enabling strong interactions with negatively charged bacterial membranes. Their primary mechanisms include membrane disruption, inhibition of intracellular targets, prevention or disruption of biofilms, and modulation of host immune responses.

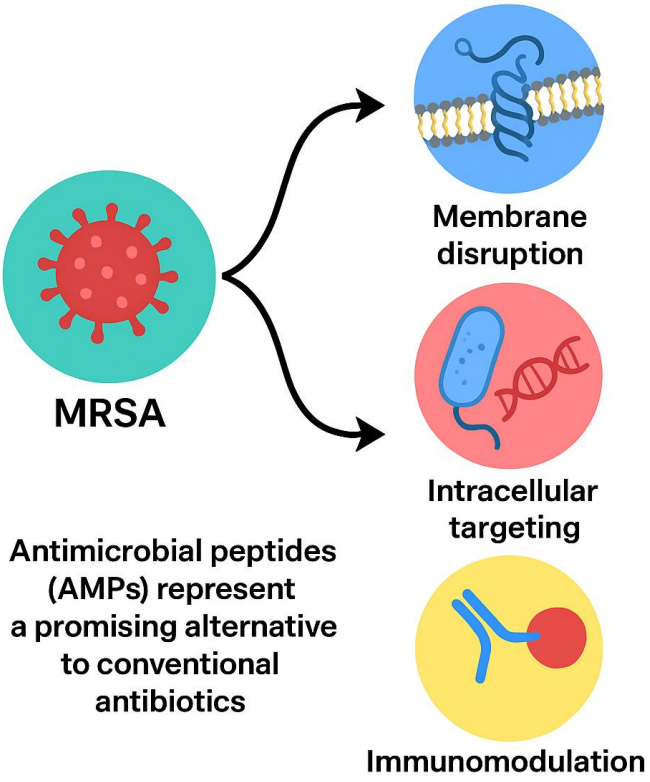

Figure 2. Mechanisms of Antimicrobial Peptides (AMPs). Schematic representation showing the multifaceted actions of AMPs, including membrane disruption, inhibition of DNA/RNA/protein synthesis, anti-biofilm activity, and modulation of host immune responses.

AMPs are ubiquitously produced across different species. Vertebrates generate defensins and cathelicidins; invertebrates produce cecropins and tachyplesins; plants synthesize thionins and defensin-like peptides; microorganisms, particularly lactic acid bacteria, produce bacteriocins. Despite structural diversity, common motifs enable antimicrobial and immunomodulatory functions, with structures including α-helices, β-sheets stabilized by disulfide bonds, proline-rich extended chains, and cyclic peptides (Mansour et al., 2014).

The advantages of AMPs over conventional antibiotics include rapid action, multi-target activity, efficacy against multidrug-resistant pathogens, and synergistic potential with antibiotics. Challenges include proteolytic degradation, cytotoxicity, and high production costs (Mahlapuu et al., 2016; Huan et al., 2020).

Given the growing need for alternatives to conventional antibiotics, various AMPs have been characterized for their anti-MRSA activity. These peptides differ in length, amino acid composition, and target specificity, offering unique advantages in combating resistant strains. To provide a concise overview of these key peptides, Table 1 lists several well-studied AMPs, summarizing their sources, primary mechanisms of action, and observed minimum inhibitory concentrations (MICs) against MRSA. It is evident that AMPs demonstrate diverse structural motifs and mechanisms, offering flexibility in therapeutic design. Their multi-target activities allow them to circumvent conventional resistance mechanisms and disrupt biofilms, addressing key challenges associated with MRSA infections. Moreover, ongoing studies on peptide engineering, including cyclization, stapling, and nanoparticle conjugation, further optimize stability, efficacy, and delivery, paving the way for the

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translation of AMPs from bench to bedside (Mahlapuu et al., 2021; Zhang & Gallo, 2021). This summary highlights the structural diversity and multifaceted activities of AMPs, which collectively contribute to their potential as effective therapeutics against multidrug-resistant infections.

Table 1. Representative Antimicrobial Peptides Against MRSA.

AMP Name	Source Organism	Mechanism of Action	MIC Range (μM)	References
WR12	Synthetic (Arginine-Tryptophan)	Membrane disruption, DNA/RNA/protein synthesis inhibition	2–8	Mohamed et al., 2016
D-IK8	Synthetic (Isoleucine-Lysine)	Membrane disruption, DNA/RNA/protein synthesis inhibition	8–16	Mohamed et al., 2016
Pexiganan	African clawed frog (Xenopus)	Membrane disruption	4–8	Mohamed et al., 2016
GW18	Synthetic (Cathelicidin-BF)	Membrane disruption, low hemolysis and cytotoxicity	Not specified	Jin et al., 2016
Lariocidin	Soil bacterium (Paenibacillus)	Inhibition of bacterial translation via ribosome interaction	Not specified	Lariocidin - Wikipedia.

Note: The Minimum Inhibitory Concentration (MIC) values are approximate and may vary based on experimental conditions and bacterial strain. For detailed methodologies and specific strain information, please refer to the cited references.

4. Peptide Engineering, Formulation, and Translational Challenges

To overcome natural limitations, AMPs undergo various engineering strategies. Cyclization and stapling enhance peptide stability and protease resistance. Conjugation with lipids, polymers, or nanoparticles improves delivery, reduces toxicity, and increases target specificity. Rational design and computational modeling enable optimization of sequences for potency, stability, and pharmacokinetics (Mahlapuu et al., 2021; Zhang et al., 2021).

Formulation strategies, including liposomes, hydrogels, and polymeric nanoparticles, protect peptides, enable controlled release, and facilitate diverse routes of administration. Combination therapies with conventional antibiotics can enhance efficacy and reduce required doses. Nonetheless, translational challenges remain, including manufacturing standardization, stability under physiological conditions, regulatory approval, and cost-effective production (da Cunha et al., 2022).

To illustrate these advanced strategies, **Figure 3** provides a comprehensive overview of AMP engineering and delivery approaches. The diagram depicts how cyclization, stapling, and sequence optimization improve peptide stability and activity, while conjugation with lipids, polymers, or nanoparticles enhances targeted delivery and reduces toxicity. Additionally, the figure highlights formulation techniques such as liposomes, hydrogels, and polymeric nanoparticles, which protect peptides, enable controlled release, and facilitate various administration routes. This visual summary underscores the integrated approach required to overcome natural limitations of AMPs and address key translational challenges in therapeutic development.

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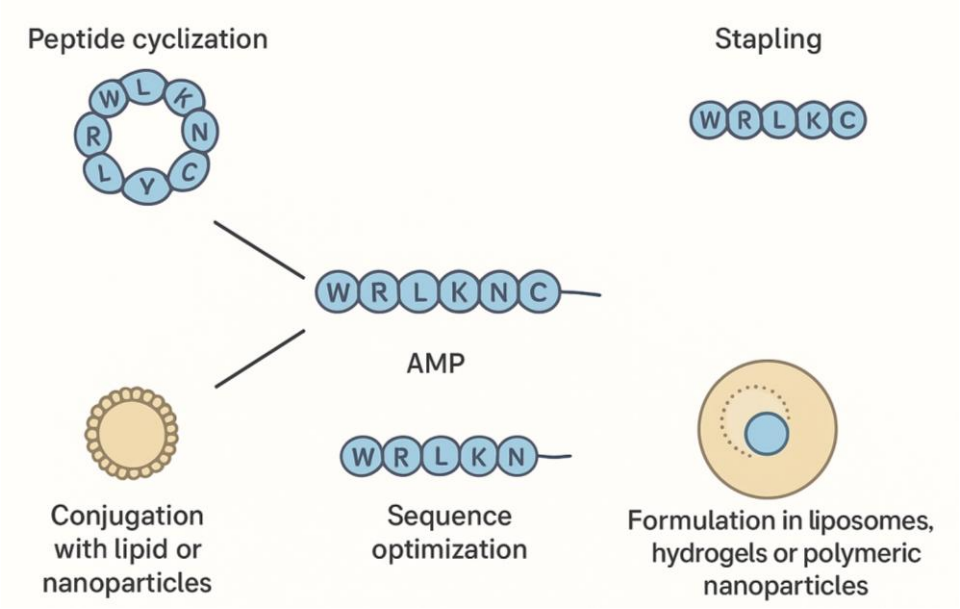

Figure 3. AMP Engineering and Delivery Strategies. Overview of key approaches to enhance AMP stability, activity, and targeted delivery, including peptide cyclization, stapling, sequence optimization, conjugation with lipids or nanoparticles, and formulation in liposomes, hydrogels, or polymeric nanoparticles.

4. Emergence of Resistance to Antimicrobial Peptides (Figure 4)

Antimicrobial peptides (AMPs) effectively circumvent classic MRSA resistance mechanisms due to their multi-target nature. By simultaneously disrupting bacterial membranes and inhibiting intracellular targets, AMPs limit the emergence of resistant strains, while also exhibiting potent anti-biofilm activity that prevents biofilm formation, disperses established biofilms, and interferes with quorum sensing pathways (Otto, 2013). These properties make AMPs particularly valuable for treating chronic, device-associated, and biofilm-mediated infections. However, despite their broad-spectrum and multi-target mechanisms, MRSA and other pathogens have demonstrated the ability to adapt and reduce susceptibility to these agents. The evolution of resistance to AMPs is multifactorial, reflecting a complex interplay between bacterial physiology, genetic regulation, and environmental pressures (Andersson et al., 2016). Bacteria can modify their cell surface by altering membrane phospholipid composition or incorporating positively charged molecules, which diminishes electrostatic attraction and impedes AMP binding. In addition, the upregulation of extracellular proteases can degrade peptides before they reach their targets, while efflux pumps actively transport AMPs out of the bacterial cytoplasm, reducing intracellular concentrations to sublethal levels. Biofilm formation further contributes by sequestering AMPs within the extracellular polymeric matrix, creating a protective microenvironment with reduced metabolic activity and enhanced stress responses. MRSA can also activate stress-response regulatory pathways, including the GraRS and VraRS two-component systems, to induce adaptive modifications that confer transient or stable tolerance to AMPs (Peschel & Sahl, 2006).

Collectively, these strategies illustrate that, despite their advantages, AMPs are not entirely immune to resistance, highlighting the ongoing evolutionary “arms race” between antimicrobial peptides and bacterial pathogens. Understanding these mechanisms is essential for guiding the rational design of next-generation AMPs, which may include sequence optimization, cyclization, incorporation of non-natural amino acids, or combination therapies to minimize the likelihood of adaptive resistance. Figure 3 schematically summarizes these known MRSA strategies to evade AMP activity, highlighting the ongoing evolutionary “arms race” between antimicrobial peptides and bacterial pathogens.

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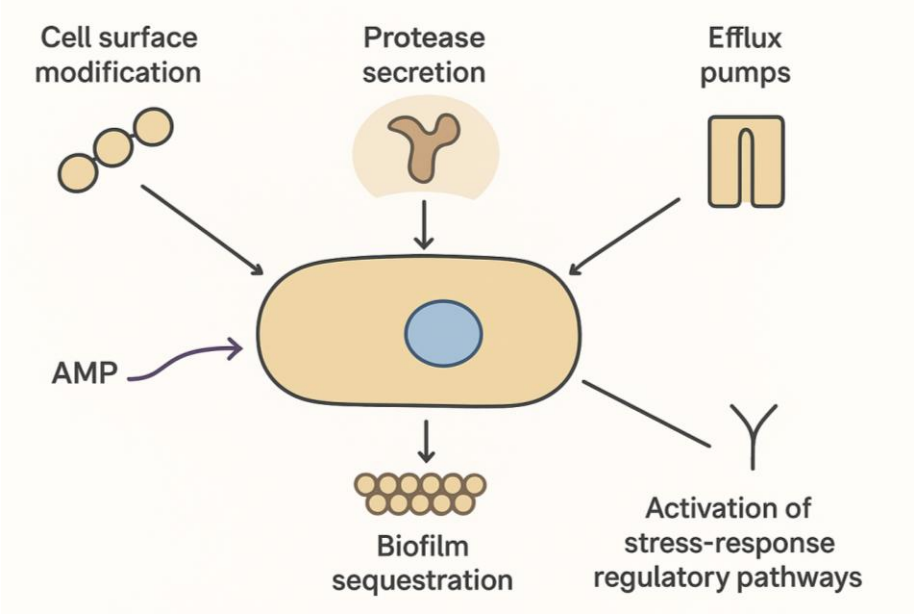

Figure 4. Emergence of MRSA Resistance to Antimicrobial Peptides. Schematic representation of MRSA strategies to evade AMPs, including cell surface modification, protease secretion, efflux pumps, biofilm sequestration, and activation of stress-response regulatory pathways.

5. Clinical Potential and Future Perspectives

Preclinical studies demonstrate AMPs' efficacy against MRSA, both in vitro and in animal models. However, translating these findings to clinical applications remains challenging. Pharmacokinetic issues, potential cytotoxicity, high production costs, and regulatory hurdles have slowed clinical progress. Current strategies focus on rational peptide design, high-throughput screening, and advanced delivery systems to overcome these barriers. Synergistic therapies combining AMPs with antibiotics or immunomodulators show promise against multidrug-resistant infections (Magana et al., 2020).

Future research should integrate computational approaches, such as machine learning and molecular modeling, to design optimized AMPs with enhanced stability, specificity, and potency. Personalized medicine approaches may also enable tailored AMP therapies for high-risk patient populations. Addressing pharmacokinetics, toxicity, and production costs will be crucial for clinical translation. Ultimately, AMPs have the potential to complement or replace traditional antibiotics in the post-antibiotic era (Huan et al., 2020; Mahlapuu et al., 2021; Zhang et al., 2021).

6. Conclusion

Antimicrobial peptides represent a promising class of therapeutics against MRSA due to their multi-target mechanisms, rapid action, and reduced potential for resistance development. Advances in peptide engineering, formulation, and delivery technologies enhance their clinical potential. However, the emergence of adaptive resistance mechanisms in MRSA underscores the need for careful design, optimization, and combination strategies to sustain efficacy. Ongoing research integrating rational design, in vivo validation, and combination therapies is critical for translating AMPs from bench to bedside, offering a viable alternative to traditional antibiotics in combating multidrug-resistant infections.

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Conceptualization, Literature Search, Data Extraction, Writing—Original Draft, Final Approval of Manuscript. All authors have read and agreed to the published version of the manuscript.

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Use of Artificial Intelligence (AI):

ChatGPT (OpenAI) was used to assist in grammar and language refinement. No AI tool was involved in data analysis, interpretation, or drawing scientific conclusions. All content was critically reviewed and validated by the authors.

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