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# Mechanisms of Bacterial Resistance to Host Defense Molecules

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## Abstract

In an attempt to keep ahead of bacterial evolution of resistance, new antibiotics based on host defense molecules or antimicrobial peptides (AMPs) produced by all multicellular organisms are being developed. Endogenous host defense molecules are among the most ancient and efficient components of our innate immune system against pathogenic microorganisms. Moreover, many AMPs employ sophisticated and dynamic mechanisms of action to exert rapid and potent antimicrobial activities. In balance, successful microbial pathogens have evolved countermeasures to protect themselves and limit the effectiveness of these antimicrobial molecules. This has led to the development of bacterial antimicrobial resistance against various AMPS, which includes diverse mechanisms like altered cell surface charge, active efflux, production of proteases or trapping proteins, and modification of host cellular processes. This comprehensive review outlines major mechanisms of resistance in both Gram-positive and Gram-negative bacteria. Understanding the genetic and biochemical mechanisms of such antimicrobial adaptation is crucial to tackling the rapid spread of resistance. Elucidating the underlying principles of this process could help in the development of more sustainable antimicrobials.

**Keywords:** antimicrobial peptide, bacterial resistance, cationic peptides, pathogen, resistance mechanism

The innate immune system represents our body's first line of defense against bacterial colonization and infection. Factors such as prevention of bacterial adherence to mucous membranes (ciliary movement, mucus, etc.), limitation of bacterial multiplication, recognition of bacterial molecules by immune cells ('pattern recognition receptors') in order to eliminate invading microorganisms and activation of adaptive immune responses if necessary are very critical in early stages of infection (Browne et al, 2020). Antimicrobial molecules are one such defensive tool deployed by the host against different bacteria. Antimicrobial peptides (AMPs), lactoferrin, bacteriolytic enzymes such as lysozyme or the group IIA secretory phospholipase A2 (PLA2) etc., are some of the host defense molecules that are very specific for microbial target structures to limit damage of human cells.

Bacterial cell surfaces have anionic net charge, which differs from those of higher organisms with cationic charge. In Gram- negative bacteria the lipid A part of the lipopolysaccharide (LPS), in Gram- positive bacteria cell wall polymers such as teichoic acids, peptidoglycan, and most of the phospholipids are negatively charged. On the contrary, virtually the entire antimicrobial host factors are positively charged. AMPs seem to represent one of the most promising future strategies for defeating this threat. They are an evolutionarily conserved component of the innate immune response, which is the principal defence system for the majority of living organisms and are found among all classes of life ranging from prokaryotes

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to humans (Zasloff, 2002). Membrane damage is considered to be the primary antimicrobial mechanism of AMPs and they preferentially act on the microbial membrane by electrostatic and hydrophobic interactions. This is due to the fact that the cationic charge of the AMPs enables them for initial interaction of the peptide with the anionic head groups of the bacterial membrane lipids. In addition, their amphipathic nature allows them to integrate into the hydrophobic core of the membrane (Peschel and Sahl, 2006). In order to survive on and within the host, bacterial pathogens use a variety of virulence factors to combat host immune system and colonize the nutrient-rich tissues of multicellular organisms. Bacterial pathogens use very efficient strategies to circumvent and misguide these host defenses in order to colonize and invade human tissues. Such host-pathogen interactions are a result of mutual inhibition, evasion and adaptation strategies that have evolved over millions of years. The key issues in microbial infection- adherence to, and invasion of, host cells, and evasion of host defences, on one hand, and the host strategies to prevent microbial colonization and tissue damage on the other are a result of ongoing, highly dynamic co-evolutionary processes. As a consequence of their need to identify niches that aid their survival and replication, most infectious microorganisms are highly adapted to specific hosts. The delicate balance between host and pathogen can be disturbed with potentially devastating consequences when pathogens adapt to a new host, as occurred during the plague, HIV and SARS epidemics (Baindara et al, 2020; Bechinger & Gorr, 2017). However, our current knowledge of the directions of host-pathogen co-evolution is surprisingly limited, even though a deeper understanding of this area could be of pivotal importance in devising methods to interfere with both old and newly emerging pathogens. This article discusses the possible microbial resistance mechanisms involved in host-pathogen adaptation with regard to the production of antimicrobial molecules by the host.

**Mechanism of bacterial resistance against AMPs**

*Nature hates monoply. . .every excess causes*
*a defect - every defect an excess. . .*

Ralph Waldo Emerson

The evolution of resistance to human AMPs may have much more serious consequences than that observed in case of evolution of resistance to conventional antibiotics. Our ability to resist infection might be permanently compromised because we ourselves are the producers. Although AMPs have a unique mode of antimicrobial action, there are instances where bacteria can lessen the impact of these peptides by virtue of intrinsic mode of resistance due to stable structural or functional properties or pathogenesis strategies or have evolved ways to overcome the lethal action of the AMPs. AMP resistance genes exist in many microbial species, making the resistance mechanisms to AMPs one of the most major obstacles ahead of exploiting AMPs for healthcare purposes (Moravej et al, 2018). According to some studies there are two fundamentally distinct strategies employed for AMP resistance: (i) passive resistance, that pertains to responses to environmental conditions, which are normally expressed independently in the absence of AMPs and (ii) inducible or adaptive resistance mechanisms that pertains to molecular modifications in bacteria induced by the presence of the AMP or the stress they cause both in Gram-negative and Gram-positive bacteria. (Abdi et al, 2019).

AMPs are produced not only by host cells but also by some staphylococcal strains. These molecules are called bacteriocins and like other AMPs, they too have a cationic, amphiphilic structure and the capacity to form pores in the bacterial CM (Hancock et al, 2016). Bacteriocins may provide a competitive advantage in nutrient-poor environments by inhibiting closely related bacteria. Many species express an outer membrane that lacks the

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appropriate density of acidic lipids to provide peptide-binding sites like *Morganella* and *Serratia*. Other resistant species, such as *Porphyromonas gingivalis*, secrete digestive proteases that destroy peptides (Zasloff, 2002; Giuliani et al, 2007). Resistance to AMPs seems to vary greatly in specificity: in some cases, it is highly specific and protects bacteria against only a narrow range of host peptides, whereas other cases involve mechanisms that confer broad resistance to many types of AMP. The yeast mutants studied by Thevissen et al., 2000, for example, were cross-resistant to other defensins - which are structurally similar to insect AMPs, but not to chemically unrelated antifungal agents. In a similar fashion, plasmid pSK1 of *S. aureus* confers resistance to human platelet microbicidal protein 1 via the efflux protein encoded by qacA, but not to nisin or neutrophil α-defensin (Kupferwasser et al., 1999). Genes that mediate resistance to epidermin in *S. epidermidis* also mediate resistance to the similar peptide gallidermin from *S. gallinarum*, but not to the less similar lantibiotic nisin or the insect AMP melittin (Otto et al., 1998). Nisin-resistant Listeria and Clostridium, on the other hand, are cross-resistant to chemically unrelated bacteriocins (Crandall & Montville, 1998).

Here we review our current understanding of mechanisms that human pathogens have evolved to resist AMP killing. Research studies on antimicrobial agents have revealed a great diversity of viable strategies for avoiding AMP killing, which include modification of the structure or the net charge of cell walls and cytoplasmic membranes, decreased affinity through cell surface alterations, external trapping mechanisms, cleaving them with the help of proteases, peptidases, creating membrane efflux pumps, downregulation of host AMP production producing exopolymers and biofilm constructing molecules, and inducing the expression of specific genes (Joo et al, 2016). Some of these basic mechanisms of bacterial resistance to AMPs are discussed below-

***Synthesis of capsular polysaccharides***

A possible way that bacteria might utilize to protect them from the host immune response is by encasing themselves in elaborate extracellular matrices, which they produce themselves. For example, *S. epidermidis* produces cationic exopolymer polysaccharide intercellular adhesion (PIA) and anionic poly-γ-glutamic acid (PGA). Both of them were found to play a role in imparting resistance to LL-37, HBD3 and anionic defense peptide dermicidin (Vuong et al, 2004; Kocianova et al, 2005; Koprivnjak and Peschel, 2011). The resistance mechanism of these polysaccharide matrices probably involves both electrostatic and mechanical (charge-independent) sequestration of host defense peptides, not related to their ultimate bacterial CM targeting (Koprivnjak and Peschel, 2011).

***Transporters***

*Staphylococcus epidermidis* strains producing the lantibiotic epidermin encode an additional protective system that encodes three genes, epiF, epiE and epiG. They expel harmful peptides from the membrane once they have entered the lipid bilayer as shown in Figure 1 below (Peschel and Collins, 2001). In this way they mediate resistance to epidermin and to closely related gallidermin from *Staphylococcus gallinarum*. These ATP-dependent translocases (Epi F, E and G) mediate either the uptake or secretion of substrate molecules and have the conserved architecture of channel-forming integral membrane and cytoplasmic domains, which is common with conserved ATP-binding cassettes (Higgins, 1992).

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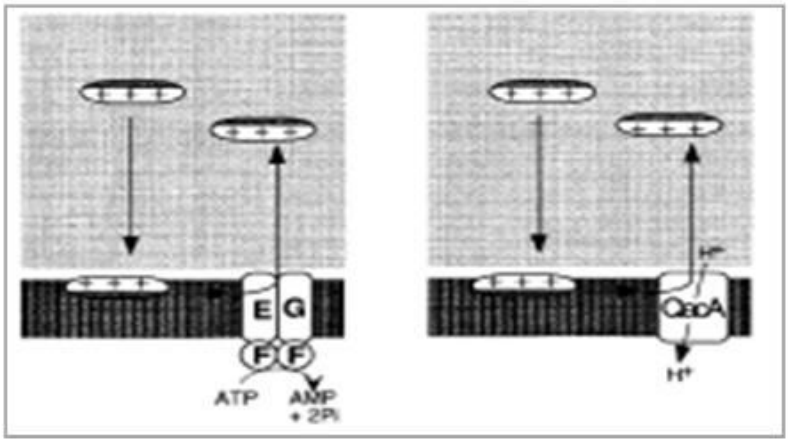


**Figure 1**: Staphylococcal cells expressing the ATP-dependent EpiFEG exporter expel the AMPs epidermin or gallidermin from the CM thereby keeping the peptide concentration in the membrane below a critical threshold. Adopted from Peschel and Collins, 2001.

***Extracellular mechanisms***

One of the adaptations that allow certain pathogenic bacteria like *S. aureus* to avoid killing by AMPs is that they bind and neutralize the AMP. This can be either direct through the actions of a bacterial surface-associated or secreted protein or indirect by the induced release of AMP binding molecules from the host cell surface as shown in Figure 2. *S. aureus* can also produce some exoproteins called staphylokinase, that does binding of plasminogen that facilitates invasion of tissues and also forms complexes with α-defensins (hNP 1-3), which results in almost 80% reduction in activity of AMPs against *S. aureus*. *Streptococcus pyogenes* produces two secreted proteins, streptococcal inhibitors of complement (SIC) and the cell wall-anchored M1 protein that bind LL-37 and other cationic AMPs with high affinity and thus prevent them from accessing the bacterial CM (Nizet, 2006). Bacteria can also prevent AMPs from reaching their target-the bacterial CM, using a cell envelope-associated or secreted proteases or peptidases that cleave AMPs and abolish their antimicrobial activity. The simple linear structure of α-helical structure of AMPs such as LL-37 is relatively susceptible to proteolysis and several microbial proteases. Examples of such secreted proteases in *S. aureus* include V8 and aureolysin proteases (Sieprawska-Lupa et al, 2004). *Salmonella enterica* serovar *Typhimurium* produces outer-membrane protease PgtE that inactivates LL-37 and contribute to bacterial survival during exposure to this peptide (Guina et al, 2000).

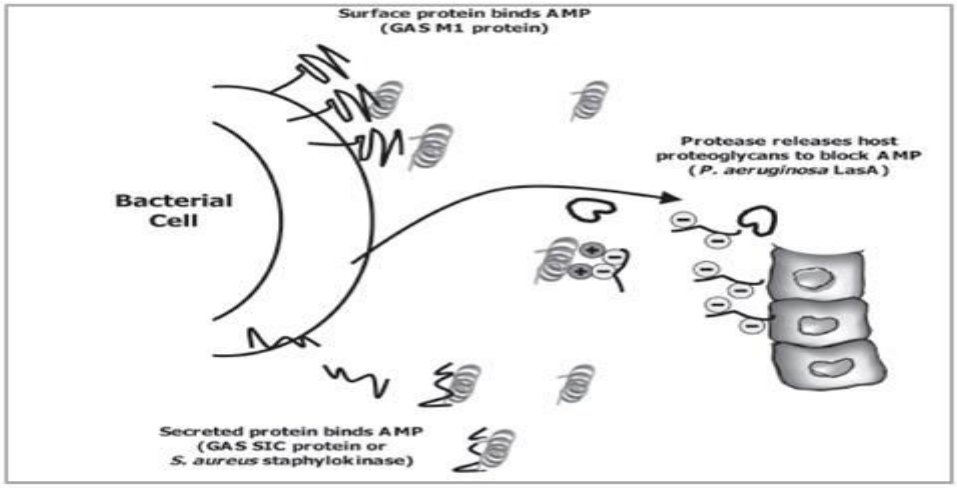


**Figure 2**: Bacterial resistance to cationic AMPs mediated by mechanisms for trapping and inactivation. Adopted from Nizet, 2006.

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***Role of teichoic acid (TA) in resistance to AMPs***

For AMPs to reach their membrane target in Gram-positive bacteria, they have to traverse the thick cell envelope. Therefore, the density and physicochemical properties of the cell envelope plays a key role in the bacterial susceptibility to antimicrobial substances (Peschel and Collins, 2001). The staphylococcal cell wall contains teichoic acids in addition to peptidoglycan and cell wall-associated protein polymers. They are polyanionic because of the abundance of phosphate groups in repeating structure (Nizet, 2006). It has been postulated that bacteria can modulate the anionic net charge of the cell envelope to reduce interactions with cationic AMPs. Most teichoic acid-producing bacteria like *S. aureus* esterify the polymers with D-alanine leading to reduction in cell wall negative charge and a partial neutralization (Peschel and Collins, 2001). This in turn repels cationic AMPs before they can reach their target of the action (Peschel, 2002; Nizet, 2006) as shown in Figure 3. Four proteins, encoded by a single operon *dltABCD*, are necessary for D-alanylation of both WTA and LTA (Koprivnjak and Peschel, 2011).

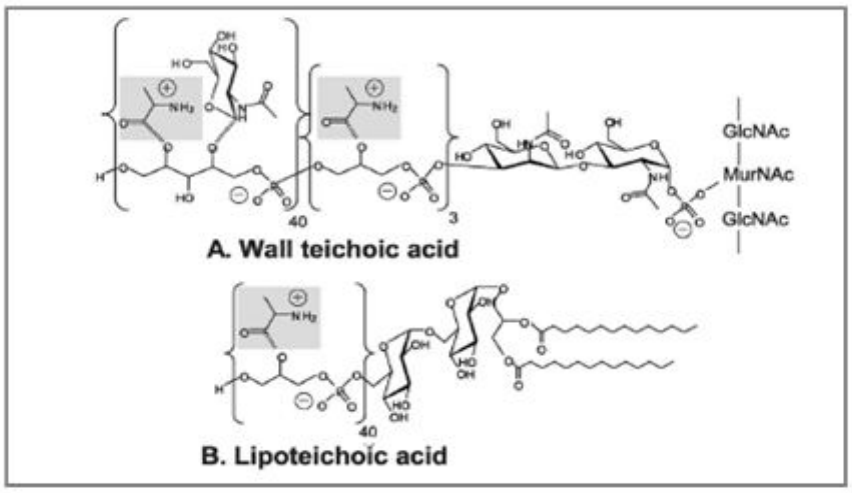


**Figure 3**: Modifications of staphylococcal cell envelope components (A) WTA and (B) LTA, involved in resistance to cationic AMPs. The D-alanine esters in teichoic acids are indicated in gray boxes. Adopted from Peschel, 2002.

***Charge neutralization of membrane phospholipid***

In bacteria, the AMPs have to negotiate and traverse enveloping structures of varying complexity to reach the principal site of action i.e., the CM (Nizet, 2006). Just like the D-alanylation of teichoic acid, *S. aureus* uses a similar concept to reduce the net negative charge of the major membrane phospholipid, phosphatidylglycerol (PG) and convert into a net positive charge by modification with L-lysine (Peschel et al, 2001). This is catalysed by the membrane protein MprF and the gene encoding this enzyme is present in many bacterial genomes and is considered to represent a widespread microbial AMP-evasion strategy (Weidenmaier et al, 2003; Peschel and Sahl, 2006). MprF (multiple peptide resistance factor), a novel integral membrane bifunctional protein of 97 kDa is highly conserved in Gram-positive and -negative pathogens (Peschel et al, 2001). It is composed of two functional domains. A well-conserved hydrophilic cytoplasmic C-terminal domain is responsible for the synthesis of lysyl-PG at the inner leaflet of CM using PG and lysyl-tRNA as substrates, representing MprF synthase (Staubitz et al, 2004; Ernst et al, 2009). Another domain is a large hydrophobic one found at the N-terminus. It consists of 14 transmembrane domains in

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*S. aureus* and many other bacteria as well. This domain is responsible for translocation of lysyl-PG to the outer leaflet of CM, representing MprF translocase (Ernst and Peschel, 2011) as shown in Figure 4 below. The two free amino groups of the L-lysine moiety of LPG give the molecule a net positive charge, in contrast to the other staphylococcal phospholipids PG and di-PG (DPG) or cardiolipin (CL), which are anionic (Peschel, 2002). It has been found that although the first eight transmembrane domains of *S. aureus* MprF were dispensable for full-level LPG production, AMP resistance was achieved only when the N-terminal domain was present. On the other hand, the N-terminal domain conferred AMP resistance only in the presence of LPG but not alone. Most of the LPG produced in the absence of the N-terminal domain was found in the inner leaflet of the CM. Even distribution between the two leaflets was found only when the N-terminal domain was present (Ernst and Peschel, 2011).

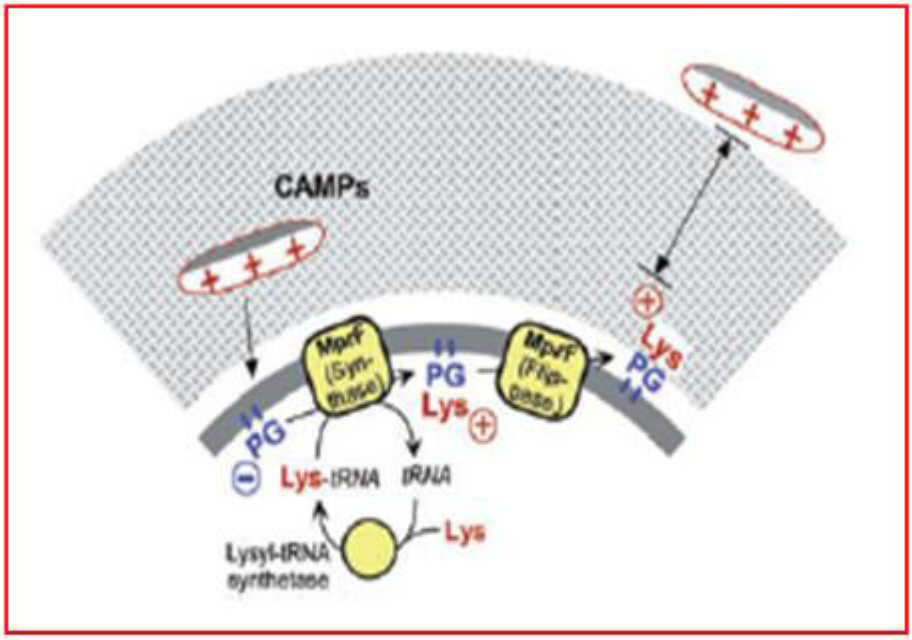


**Figure 4**: Mode of action of *S. aureus* MprF. Lys-PG is synthesized from Lys-tRNA and PG by the synthase domain of MprF. Lys-PG can only neutralize the outer surface of the membrane upon translocation to the outer cytoplasmic membrane leaflet, which is facilitated by the flippase domain of MprF. Adopted from Ernst and Peschel, 2011.

MprF has also been shown to be under control of ApsRSX regulator. MprF mutants show increased sensitivity to killing by cationic AMPs, and neutrophils and are also virulence-attenuated in multiple animal models (Weidenmaier et al, 2005; Peschel et al, 2001; Koprivnjak and Peschel, 2011). Increased LPG content and point mutation resulting in MprF gain-in-function have been recently reported to increase resistance to daptomycin *in vitro* and *in vivo* (Friedman et al, 2006; Rubio et al, 2011; Yang et al, 2009; Koprivnjak and Peschel, 2011). In addition, mprF affects sensitivity to several other antibiotics such as gentamicin, vancomycin, and moenomycin.

***Alteration of outer membrane***

In Gram-negative bacteria, the cell envelope has an outer membrane instead of a cell wall. The composition of Gram-negative outer membrane is lipopolysaccharides (LPS). Lipid A, the anionic component of LPS consists of two glucosamine units with free phosphate groups linked to four or more acyl chains (Raetz et al, 2007). *Salmonella* can reduce the net negative charge by modifying lipid A and LPS core sugars by incorporating aminoarabinose or phospho-ethanolamine. This leads to increased resistance to the cationic AMPs like polymyxin B (Gunn, 2001; Koprivnjak and Peschel, 2011). The genes responsible for

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modification of lipid A by aminoarabinose (*pmrEHFIJKL*) and ethanolamine (*pmrC*) are under control of PmrAB two-component system. The activity of the PmrA transcriptional regulator is controlled by two different systems: (a) a sensor kinase PmrB that senses iron, zinc and mild acidic conditions and (b) PhoPQ two-component system, that regulates PmrA activity through PmrD protein (Koprivnjak and Peschel, 2011).

***Changes in membrane fluidity***

Changes in membrane fluidity have also been shown to influence cationic AMP resistance in Gram-positive organisms and fungus (Abe and Hiraki, 2009; Bayer et al, 2000; Kang and Park, 2010; Mishra et al, 2009 and 2011; Xiong et al, 2005). Bacterial membranes that are composed predominantly of saturated fatty acids tend to be relatively rigid and unsaturated fatty acids promote lipid disorder and thereby increase membrane fluidity (Bayer et al, 2000; Shireen et al, 2012). Incorporation of longer chain unsaturated fatty acids in membrane lipids results in an increased membrane fluidity and resistance of *S. aureus* to platelet derived cationic AMP (Koprivnjak and Peschel, 2011). It has been postulated that for each specific AMP and bacterial membrane interaction, there is an optimum relative membrane order at which AMPs exert maximum activity (Mishra et al, 2009). Extremes of membrane rigidity or fluidity account for non-susceptibility to many AMPs. Altered membrane order is an adaptation under the continuous selective pressure of the peptide and this could possibly be due to shifts in fatty acid unsaturation indices or branched chain species. Several studies also suggested the role of pigment production in *S. aureus* in influencing sensitivity to cationic AMPs. Recently Mishra et al, discovered that increased production of carotenoid staphyloxanthin in *S. aureus* increases its resistance to human neutrophil defensin 1, platelet-derived cationic AMPs, and polymyxin B by increasing membrane rigidity (Mishra et al, 2011; Koprivnjak and Peschel, 2011). Why extreme increase and extreme decrease in membrane fluidity lead to increased resistance to cationic AMPs is still under investigation. However, it appears that the mechanism of resistance may be specific for different AMPs (Koprivnjak and Peschel, 2011).

***Expulsion of AMPs***

Even after AMPs have attached to and inserted in the cytoplasmic membrane, bacteria can remove them using effective efflux pumps, which constitute another important AMP resistance component. Efflux pumps are complexes of mostly membrane bound proteins that move toxic compounds out of cells. These pumps are divided into two different types based on their mechanisms of action: type 1 includes primary transporters that extrude AMP by ATP hydrolysis, and type 2 includes secondary transporters that function by transmembrane electrochemical gradients of either protons or sodium ions. (Levy, 2002; Nizet, 2006). *Neisseria gonorrhoeae* utilizes the MtrCDE multidrug resistance (MDR) exporter to expel different antibiotics and confer resistance to the cationic AMPs protegrin PG1 and LL-37. Certain *S. aureus* strains harbour a multiresistance plasmid pSK1 that encodes the QacA efflux pump. Resistance mediated by *S. aureus* MDR exporter QacA to rabbit tPMP has been suggested not to be associated with the ability of QacA active transport of cationic AMP but rather attributed to the secondary QacA mediated changes on membrane fluidity (Kupferwasser et al, 1999; Koprivnjak and Peschel, 2011).

***Biofilm formation***

Bacteria can further resist AMPs by organizing into specialized structures known as biofilms. Bacterial biofilm is a consortium of surface-attached bacterial cells that are embedded in a matrix composed mainly of extracellular proteins, extracellular DNA and exopolysaccharides (EPS). The slimy exopolysaccharides secreted by the bacteria help them to attach to the

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surfaces, and act as a barrier against invading entities and repel AMPs (Band, & Weiss, 2015). The *P. aeruginosa* biofilm contains the polysaccharide alginate, which is an acylated polysaccharide comprising anionic sugars (e.g., glucuronic acid and mannuronic acid) that binds to AMPs and induces conformational changes in their structure. Anionic alginate in *P. aeruginosa* not only contributes to biofilm structure but can also bind to and induce conformational changes in invading CAMPs. Polysaccharide intercellular adhesin (PIA, also known as poly-N-acetyl glucosamine), which is produced by *S. aureus*, *S. epidermidis*, and a variety of other bacteria including other staphylococci and *E. coli*, is responsible for resistance to cationic HBD-3 and LL-37 as well as anionic dermcidin. The action of PIA can be augmented by deacetylation, causing an enhanced net positive charge of the biofilm matrix. Thus, biofilms intrinsically complicate the use of AMPs for the treatment of infections caused by biofilm-producing bacteria (Sierra et al, 2017).

**Conclusion**

During the past few decades, it has become evident that increasing bacterial drug resistance has created an urgent need for new classes of antimicrobials. AMPs seem to represent one of the most promising future strategies for defeating this threat. They are an evolutionarily conserved component of the innate immune response, which is the principal defence system for the majority of living organisms and are found among all classes of life ranging from prokaryotes to humans. However, microbial pathogens have evolved constitutive or `inducible countermeasures to subvert antimicrobial peptide mechanisms of action. The structure-activity themes of AMPs are consistent with their likely multiple roles in antimicrobial host defense. However, many such resistance pathways are highly coordinated and triggered by exposure to AMPs themselves. Thus, a more thorough understanding of the balance between the opposing mechanisms of action and resistance among AMPs will further reveal how these molecules function to defend against infection. Improved knowledge of the molecular basis of these bacterial escape mechanisms may identify novel targets for antimicrobial therapy. Such drugs could act to block bacterial cell wall modifications, efflux pumps, or inactivating factors, thereby rendering the organisms sensitive to the natural innate immune defense provided by AMPs. From these perspectives, the mechanisms of antimicrobial peptide action and resistance may hold many secrets yet to be uncovered or fully appreciated.

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