

Antimicrobial Peptides as Anti-Infectives against *Staphylococcus epidermidis*

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Key Words

Biofilm · Pathogenesis · Synthetic peptide

Abstract

Staphylococcus epidermidis has emerged as the main causative agent for graft-related and nosocomial infections. Rampant use of antibiotics and biofilm formed by the organism results in poor penetration of the drug and further aggravates the antibiotic resistance, emphasizing an urgent need to explore alternative treatment modalities. Antimicrobial peptides (AMPs), produced as effector molecules of the innate immunity of living organisms, have therapeutic potential that can be used to inhibit the growth of microbes. In addition, the susceptibility of a microbe to become resistant to an AMP is relatively low. The AMPs are amphipathic peptides of 12–100 residues, which have broad-spectrum activity against microbes. There are scattered reports of AMPs listed against *S. epidermidis* and there is an urgent need to systematically study the AMPs. Various natural AMPs as well as synthetic peptides have been investigated against *S. epidermidis*. These peptides have been shown to inhibit both planktonic culture and *S. epidermidis* biofilm effectively. The multiple modes of action in killing the organism minimize the chances for the development of resistance. This review focused on various natural and synthetic peptides that demonstrate activity against *S. epidermidis*.

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Introduction

Staphylococcus epidermidis is a Gram-positive bacteria and a coagulase-negative staphylococcus [1]. *S. epidermidis* forms a part of the skin flora and is also found in the mucous membrane of animals [2] and may penetrate the epithelial barriers of the human body. It has been reported for superficial infections within the sebaceous gland [3]. It is a major causative organism of infections related to implanted medical devices and it is also involved in nosocomial infections (hospital-acquired infections) [4]. Furthermore, it has been identified as one of the major blood culture contaminants [5]. Therefore, it is also named as a nosocomial pathogen or an opportunistic pathogen [6].

S. epidermidis infections mainly occur due to prolonged hospitalization, several surgical procedures during the time of implant and/or infections in other parts of the body. The major entry points of *S. epidermidis* are skin at the insertion site of the implanted medical device, colonization of the device before implant, microbes shed off from health care workers and airborne contamination. The kind and complexity of the infection depend upon the insertion site and the type of medical device that is introduced. The chance of infection is comparatively high in immunocompromised critically ill patients [2]. There are various factors that influence the pathogenesis

of *S. epidermidis*. Some of these include biofilm formation, secretion of extracellular enzymes and toxins, interference with the host innate immune system and intracellular persistence. The main factor responsible for the pathogenesis of *S. epidermidis* is for the most part attributed to its ability to attach to the surface and proliferate there [7]. The resultant biofilm formed by the organism undergoes variation at a genetic level and is more resistant to treatment by antibiotics compared to its planktonic culture [1].

Misuse of antibiotics, incorrect diagnosis and over-the-counter availability have resulted in an incessant exposure to antibiotics, posing a hurdle for the treatment of *S. epidermidis* infections [4]. *S. epidermidis* has shown resistance to many antibiotics such as methicillin, aminoglycosides, macrolides and, to a lesser extent, tetracycline, chloramphenicol and clindamycin, as well as intermediate resistance to vancomycin [8]. Biofilm formed by *S. epidermidis* has also shown resistance and decreased penetration to antibiotics such as oxacillin, cefotaxime (β -lactams) and vancomycin (a glycopeptide) [9]. Biofilm formation, being one of the key reasons for disease manifestation, is being targeted for therapy. Various approaches like quorum-sensing interference [10, 11], immunotherapy [12], enzymatic removal [13], immunomodulation [14] and inhibition of bacterial growth by antimicrobial peptides (AMPs) and certain plant and synthetic compounds [4] are being studied.

This review focuses on AMPs as effective agents for the control of *S. epidermidis* infections because it has been shown that *S. epidermidis* biofilm is sensitive to these amphiphilic peptides and can help to protect implants from bacteria and alleviate nosocomial infection [4].

***S. epidermidis* Biofilm Formation**



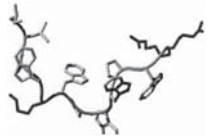
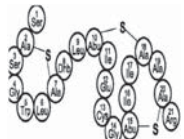
Biofilm is defined as the accumulation and subsequent proliferation of cells in a matrix of extracellular substances to form a highly resistant network of bacteria. These bacteria get attached to the devices and then colonize them, which results in biofilm formation and thus leads to an infection, eventually causing the dysfunction of the device that was implanted. Moreover, these microbes can leave the native site of infection and infect other areas also [2].

Biofilm formation involves four stages: attachment, adhesion, maturation and detachment. In the first stage, the bacteria may get attached to the surface of the abiotic device directly, or the device first becomes coated with

biotic material (host-derived proteins) and then bacteria colonize the device [4]. The compounds involved in the attachment process include microbial surface components recognizing the adhesive matrix molecule, surface-associated autolysin AtlE, Embp (extracellular matrix protein-fibronectin binding protein) and teichoic acid [8]. During accumulation, bacteria pile on each other and form multilayered cell clusters forming a widespread network of bacteria. Intercellular adhesion, aggregation and proliferation, further enhanced by the presence of host serum proteins and adsorbed proteins, result in the formation of a mature biofilm [3]. This stage is characterized by the production of proteins such as polysaccharide intercellular adhesin (PIA), accumulation-associated protein and Bap homolog protein [9]. The maturation stage is characterized by the generation of slime glycocalyx. Slime exopolysaccharide increases the stability of the biofilm architecture, which increases its resistance. Thus, a mature biofilm consists of the substratum which provides the attachment surface for the main components of the biofilm. The lowermost part of the biofilm, called the conditioning film, is in contact with the substratum and provides nutrients to the rest of the biofilm. The linking film then connects the conditioning film to the main bulk of the biofilm, which also consists of an extracellular polymeric substance that aggregates the cells together in a protective matrix of fluid-filled channels which provide oxygen and nutrients and remove metabolic waste. The mature biofilm can disseminate individual bacterial cells that spread and colonize other suitable sites. The overall detachment stage in biofilm is controlled by the expression of surface-associated adhesins, localized shear stress, a decrease in cell viability and uncontrolled growth patterns. This process is mediated by phenol-soluble modulins and their components such as δ -toxin [4]. The quorum-sensing system plays a vital part in synchronizing gene expression and coordinating functions among bacterial networks. It uses small signaling molecules known as the autoinducers. Two quorum-sensing systems have been identified in *S. epidermidis*, which are the accessory gene regulator system and the luxS system [1].

Biofilm formation seems to be a major problem in an attempt to eradicate *S. epidermidis* infections because there are various factors that contribute to biofilm resistance. Biofilms are enclosed in an extrapolymeric matrix that mainly consists of exopolysaccharides, proteins and nucleic acids which act as physical barriers and restrict the entry of antimicrobial agents. The chemical environment (such as the pH, cation concentration and pyrimidine concentration) inside the biofilm may get altered,

Table 1. Classification of AMPs into four clusters based on their structure

Sample No.	Type of AMP	Structure	Property	Example	Basic structure	Reference
1	Type I: linear α -helical peptides	Highly positively charged Unstructured in aqueous solution, and fold into their α -helical configuration when they bind to the bacterial membrane	27% of peptides belong to this group Cationic amphipathic helices Capping at the N- and C-terminus stabilizes the helix Kill the microbes by creating channels in the membranes	Alamethicin, cecropin, magainin, LL-37		22
2	Type II: cyclic peptides with β -sheet structure	1–5 disulfide bonds Stably assembled by either disulfide bonds or cyclization of the peptide backbone	Number of disulfide bonds decide degree of cyclic conformation Exist in β -sheet conformation in aqueous solution Act on intracellular targets Enter cell by lipid flip-flop movement	Tachyplesins, defensins, protegrins, polymyxin		23
3	Type III: extended peptide	Linear in shape No secondary structure	Over representation of 1 type of amino acid Rich in proline and/or glycine, tryptophan or histidine Aggregate in the membranes and create a voltage-induced channel, the peptides are translocated into cytoplasm	Histatin (histidine), ritrpticin (arginine), dipterocins (glycine), indolicidin		24
4	Type IV: looped peptide	Looped structure due to the single disulfide, amide or isopeptide bond Antiparallel β -sheet orientation	Short in size, easy to synthesize and proteolytically stable	Lantibiotics		23

which reduces the activity of antibacterial agents [15]. *S. epidermidis*, as part of the biofilm, expresses resistance genes that might help them attain a distinct phenotype. Moreover, the presence of persister cells protects the biofilm and contributes to its resistant property to many antimicrobial agents [4].

AMPs as an Alternative Therapy

There is an urgent need to come up with alternative approaches that are effective against bacterial infections. AMPs are highly selective and effective against multi-drug-resistant pathogens, which makes them very interesting lead compounds for the development of drugs [16].

AMPs are a large group of compounds which are small-molecular-weight proteins produced by various multicellular organisms from both the vegetal and animal kingdoms [17]. The majority of AMPs have broad-spectrum activity and a net positive charge due to multiple lysine and arginine residues, as well as a large portion (>30% or more) of hydrophobic residues [18]. These are amphiphilic in nature, due to which they form clusters of

hydrophobic and hydrophilic residues [19]. To date hundreds of such AMPs are known, which are multifunctional as they not only eliminate various pathogenic microorganisms, including Gram-positive and Gram-negative bacteria, fungi, yeast, viruses and others, but also play a promising role in elements of the innate immunity system [20, 21].

AMPs: Classification and Mechanism of Action

AMPs have been elaborated on and classified on the basis of their structures (table 1). The main mechanism of killing of AMPs involves interaction with microbial membranes – its permeabilization – which leads to the outflow of cellular contents and eventually the death of the microbe [25]. Bacterial membranes are negatively charged with lipids that have phospholipid head groups such as phosphatidylglycerol, cardiolipin, or phosphatidylserine. However, mammalian membranes are made up of zwitterionic phospholipids (neutral in net charge) such as phosphatidylethanolamine, phosphatidylcholine or sphingomyelin. This is why cationic peptides can interact

with bacterial membranes and aggregate them [26]. Thus, the composition of the membrane plays a major role in the targeting process of the AMPs [18]. This multiple targeting and physical disruption of the target cell membrane make microbes less likely to become resistant to AMPs compared to conventional antimicrobials and thus become promising candidates for the generation of new anti-infective agents [27].

These AMPs may also undergo posttranslational modifications which may include proteolytic processing, and in some cases glycosylation, carboxy-terminal amidation and amino-acid isomerization, and halogenation. This kind of structural modification decreases the susceptibility of the AMP to degradation, thus increasing the stability of the peptide [28]. Cathelicidin proteins have a highly conserved cathelin domain at the N-terminus and can release an AMP from the C-terminal end after proteolytic cleavage. Cathelicidin LL-37, a 37-residue, helical and amphipathic peptide (the only member from humans), has been reported for wide antimicrobial activity [24]. Circular defensin isolated from neutrophils of rhesus monkeys involves complex modification in terms of cyclization of two short peptides. Some peptides are also derived by proteolysis from larger proteins, such as buforin II from histone 2A. The AMPs show great diversity when it comes to the peptide sequence because single mutations can dramatically alter the biological activity of each peptide. The diversity reflects the species adaptation to the unique microbial environments [28].

AMPs against *S. epidermidis*

Natural AMPs and Their Derivatives

AMPs are the characteristic features of the innate immunity of mammals, which provide a defense system against microbes by disrupting their cell membrane. Features of some of the natural peptides against *S. epidermidis* are given in table 2. Hecpudin is a cysteine-rich cationic peptide that is produced in the liver of vertebrates and also in the fat body of the insects. Park et al. [29] identified hecpudin from human urine samples and predicted that it might be a vertebrate counterpart to the cysteine-rich peptides produced in the fat body of insects such as drosophila. Hecpudins isolated from humans are 2–3 kDa and have an overall charge of +3. They are 20–25 amino acids in length, out of which 8 are cysteines and are involved in disulfide linkage due to which they belong to the class of peptides that have a cysteine knot. Moreover, they are not cytotoxic at very high concentrations and

show acceptable activity against *S. epidermidis*. Brancatisano et al. [45] have recently reported the antibiofilm activity of hepcidin 20 on both PIA-positive and PIA-negative strains of *S. epidermidis*. Hell et al. [46] have shown that human cathelicidin peptide LL-37 can inhibit the biofilm formation as well as the ability of *S. epidermidis* cells to attach to the surface. Moreover, in a recent study the same group has shown that LL-37 can reduce the expression of biofilm-related genes and decrease the biofilm growth on an in vitro model of a medical device [47].

The AMPs from amphibians, known as temporins, are a class of AMPs formerly isolated from the skin secretions of the European red frog *Rana temporaria*. The majority of temporins (temporin A, temporin B and temporin-1DRa) disrupt the cell membrane of the target cell mediated by electrostatic interactions. Temporin A has been shown to be active against both methicillin-susceptible and methicillin-resistant *S. epidermidis* and has also inhibited its biofilm formation. It was also effective in a micro-model of vascular graft infection. It exhibited minimum inhibitory concentration (MIC) of 8 mg/l and was not toxic to human erythrocytes. Temporin A may act by creating channels or pores or it may trigger the bacterial murine hydrolases, which causes disruption of the peptidoglycan layer leading to lysis of the cell. The in vivo studies conducted by Ghiselli et al. [31] showed that temporin A in combination with vancomycin hydrochloride was able to produce complete bacterial inhibition compared to antibiotic or temporin A alone.

Temporin-1DRa has potent activity against *S. epidermidis* but it shows cytotoxicity to mammalian cells. Thorough analysis of the alteration of the amino acid residues on antimicrobial activity and cytotoxicity was carried out and it was concluded that the change which increased the cationicity improved the antimicrobial potential, and the decrease in hydrophobicity and helicity reduced the hemolytic effect, contributing towards nontoxic peptide [34].

There are some natural peptides that were modified and found to be more effective in combination against *S. epidermidis*. Royal Jellein I, II and III secreted by the honeybee, *Apis mellifera*, were modified at the C-terminal to form RJ I-C, II-C and III-C, respectively. These peptides fold and aggregate into the membrane and showed anti-staphylococcal activity. A chemically modified analog of temporin (TB-KK) and RJ I-C has been used synergistically and found to be more effective against Gram-positive bacteria than their individual components [32]. These two peptides were isolated from different organisms and have different mechanisms of action: TB-KK

Table 2. Different characteristics of natural and synthetic AMPs listed from various sources against *S. epidermidis*

Sample No.	Name of AMP	Source	Sequence	Characteristics	Mechanism of action	Reference
1	Hepcidin	Liver of vertebrates	RRRRRDTHFPICIFCCG-CCHRSKCGMCKCT	Human hepcidin: 30% cysteine content, 2–3 kDa, net charge of +3 at neutral pH, consists of intramolecular disulfide bonds	Interferes with intracellular nucleic acids	29, 30
2	Temporin A	European red frog (<i>R. temporaria</i>)	FLPLIGRVLSGIL	Net positive charge, highly hydrophobic, AMP amide	Form ion-conducting and anion-selective channels	31
3	Temporin B (TB-KK)	Granular glands of European red frog (<i>R. temporaria</i>)	YLLPIVGNLLKSL KKYLLPIVGNLLKSL	α -Helix structure, nontoxic to mammalian cells	Does not aggregate into the membrane Causes the collapse of plasma membrane potential	32, 33
4	Royal Jellein I (RJ I-C, RJ II-C, RJ III-C)	Mandible and hypopharyngeal glands of honeybees (<i>Apis mellifera</i>)	PFKIDIHLGGY TPFKISIHGGY EPFKISIHGGY	β -Sheet, amidated at C-terminus, net charge of +2	Folds and aggregates into the membrane	32
5	MIX	Temporin B + Royal Jellein I-C	KKYLLPIVGNLLKSL PFKIDIHLGGY	Synergistic combination	Modulates proinflammatory cytokines	32
6	Temporin-1DRa and its analogs	California red-legged frog (<i>Rana draytonii</i>)	HFLGTLVNLAKKIL HFLKKLVLAKKIL HFLGKLNLAKKIL	α -Helix, high lysine content: net charge +3 at pH 7	Nonspecific perturbation of the membrane	34, 35
7	Ranalexin	Skin of the American bullfrog (<i>Rana catesbeiana</i>)	NHFLGGLIKIVPAMIC -AVTKKCCO	Polycationic peptide	Shows multiple killing mechanisms and affects the cell wall or the cell membrane	36–38
8	Buforin II	Derived from buforin I (<i>Bufo gargarizans</i>)	TRSSRAGLQFPVGRVHR-LLRK	Polycationic peptide	Causes the disruption of intracellular processes	36, 39, 40
9	Epidermicin NI01	<i>S. epidermidis</i> strain 224	MAAFMKLIQFLATKGQKYVS-LAWKHKGTILKWINAGQSFE-WIYKQIKKLWA	Highly cationic, plasmid-encoded peptide, globular α -helical structure	Acts by toroidal pore formation	41
10	Bactericidal peptide 2 (BP2)	SAMPs	GKWKLFFKAFKFLKIL-AC	Lipopolysaccharide binding domain, amphipathic conformation	Mediates killing by membrane disruption or pore formation	42
11	Compound 5	Derivative of thiazolidinone	NA	β -peptoid-peptide hybrid	YycG histidine kinase inhibitor	43
12	Compound 2	Derivative of thiazolidinone	[2-(4-[3-(2-ethylphenyl)-2-[(2-ethylphenyl)imino]-4-oxothiazolidin-5-ylidene]methyl)-2-methoxyphenoxy] acetic acid	Thiazolidinone core structure	YycG histidine kinase inhibitor	43
13	Derivatives of compound 2	Synthetic compounds from compound 2	NA	Thiazolidinone core structure	YycG histidine kinase inhibitor	43
14	β -Peptoid-peptide	Peptidomimetic	NA	Structural analogs of peptides, amide bond isosteres result in high stability	Pore formation and disruption of integrity of bacterial membrane	

NA = Not available.

possesses a hydrophobic domain and does not accrue onto the membrane, while RJ I-C, with a net positive charge, aggregates at the membrane. These peptides in combination showed maximum antimicrobial and anti-inflammatory activity while modulating cytokines and nitric oxide production [32].

Other polycationic peptides like ranalexin and buforin II derived from the skin of the American bullfrog and from the stomach tissue of an Asian toad, respectively, have shown broad-spectrum antimicrobial activity. Synergistic studies [33, 36] of ranalexin/buforin with cefazo-

lin were conducted by Giacometti et al. [36] to investigate the effect of polycationic peptides on methicillin-resistant *S. epidermidis* strains. The combination of ranalexin or buforin-II with cefazolin treatment proved to be more effective than cefazolin treatment alone against both methicillin-sensitive and methicillin-resistant strains. Pseudhymenochirin-1Pb (Ps-1Pb) and pseudhymenochirin-2Pa (Ps-2Pa) are host defense peptides isolated from skin secretions of the frog *Pseudhymenochirus merlini* and have been reported for their antimicrobial and anticancer activity [44].

The AMPs from plants include two peptides isolated from the garden pea plant, namely S4, a seed peptide, and P8, a pod peptide, which showed broad-spectrum antibacterial activity. Both of these peptides have been reported to be temperature, pH and protease sensitive. Both S4 and P8 exhibited antimicrobial activity at 25°C but did not inhibit *S. epidermidis* activity above this temperature. They have been reported to show a clear zone of approximately 16.6 mm by disc diffusion method [48].

The AMPs from bacteria include epidermicin NI01, which is a peptide produced by *S. epidermidis* strain 224 and shows a mode of action similar to nisin, thus qualifying as a type IIa bacteriocin (lantibiotic). It is a highly cationic peptide carrying an N-terminal-formylated methionine and exists as a globular α -helical structure. It has shown potent antimicrobial activity against multiple drug-resistant strains and biofilm-forming *S. epidermidis* strains as the peptide was found to be active even in nanomolar concentrations. Epidermicin NI01 showed high protease stability and was active even at a wide range of pH (2–10) and at a temperature of 80°C for 60 min. The open reading frame encoding the peptide, *edcA*, has been cloned and expressed in *Escherichia coli* strain BL21, and purified recombinant epidermicin was of 6,074 Da. Epidermicin consists of about 17.6% of lysine residues, which accounts for its strong antimicrobial activity, and has low hemolysis and cytotoxic capability. This peptide showed maximum activity on *S. epidermidis* MRSA isolates, with an MIC of 2–4 $\mu\text{g/ml}$. Moreover, it did not show hemolysis at 100 \times MIC [41].

Synthetic Anti-Infective Agents against S. epidermidis

The sequence of synthetic peptide could be of natural peptide, its derivative or de novo and is synthesized chemically outside the cell. During designing the undesirable sequences of a particular peptide can be removed and altered based on selectable features enhancing the effective therapeutic potential. Some of the synthetic peptides (table 2) are bacterial peptide 2 (BP2), synthetic antimicrobial peptidomimetics (SAMPs), β -peptoid peptide and derivatives of thiazolidinone, compound 2 and compound 5 [49].

BP2 is designed on the basis of the lipopolysaccharide binding domain and the ability of the sequence to form an amphipathic confirmation. Activity of this peptide was analyzed against a murine biomaterial-associated *S. epidermidis* infection. The results showed that BP2 reduced the survival of *S. epidermidis* in peri-implant tissues and also showed good stability in vivo [42].

SAMPs (Ltx5, Ltx9, Ltx10 and Kp14) are modified cationic AMPs (700–800 Da) with improved pharmacokinetic properties. All four of these peptides are tripeptides with two arginine residues which render positive charge. The lipophilic part is provided by a modified tryptophan derivative in Ltx5, Ltx9 and Ltx10, and 40-phenyl-phenylalanine in Kp14. Kp14 showed maximum activity against *S. epidermidis* with an inhibitory concentration of 256 mg/l on the RP62A strain. Ltx5 has the smallest C-terminal modification and Ltx9 has the largest. Ltx5, Ltx9 and Ltx10 effectively eliminated the metabolic activity of *S. epidermidis*, which was confirmed by complete cell death using confocal laser scanning microscopy, but Kp14 showed poor activity in a biofilm susceptibility assay. Presently, Ltx9 is in the stages of a phase I clinical trial for postoperative open-wound local therapy; thus, Ltx SAMPs are potential candidates for the treatment of *S. epidermidis* infections [50].

Derivatives of Compound 2

The recognition of the signal and the ability to respond specifically in terms of genetic alterations or behavioral changes are the essence of bacterial survival. The two-component YycG/YycF system originally identified in *Bacillus subtilis* is highly conserved and specific to Gram-positive bacteria that have a low G+C content, including *S. aureus* and *S. epidermidis*. They play an important role in regulating virulence and cell wall metabolism and, being essential for organism growth, serve as a target for inhibition [51]. Two such inhibitors, compounds 2 and 5, derivatives of thiazolidinone, have been designed for the YycG/YycF system. Compound 2 is an YycG histidine kinase inhibitor which has the capability to disrupt the biofilm structure. Compounds 2 and 5 target the histidine kinase YycG domain of *S. epidermidis*; they have shown bactericidal activity and have also exhibited high activity in a biofilm dispersal assay. These two compounds have been found to be effective against methicillin-resistant *S. epidermidis* planktonic cells. The activity of compounds 2 and 5 was found to be more efficacious than vancomycin during the early period of exposure. When compound 5 was used along with vancomycin, the antimicrobial activity against *S. epidermidis* was enhanced but the activity of compound 2 remained unaffected in combination with vancomycin [43].

Derivatives of compound 2 were synthesized by modifying the functional groups through cyclization, aldol condensation and substitution and hydrolyzation reactions, and shown to be YycG inhibitors. Further research has been carried out for compound 2 and its derivatives

have been designed keeping the thiazolidinone core structure intact, which are more effective and less toxic than compound 2. Although compound 2 and its derivatives have been validated, the derivatives of compound 5 have yet to be researched and the most stable and effective compound still needs to be discovered [39]. Their mechanism of killing is different as they may translocate across the membrane, build up inside a bacterial cell and interfere with the essential intracellular processes, such as the inhibition of nucleic acid synthesis, the translation, replication and activity of several enzymes, and the inhibition of cell wall synthesis, and eventually mediate bacterial cell death [23].

Of compounds 2 and 5, compound 2 showed higher bactericidal activity of about 100 μM against the RP62A strain. Moreover, mammalian cells do not have genes homologous to YycG/YycF, so these derivatives are not cytotoxic to mammalian cells. However, Gram-positive bacteria have a highly conserved YycG/YycF two-component system, which makes these anti-YycG compounds highly effective [52].

Conclusion

The increasing trends of antibiotic-resistant pathogens have long been recognized as a significant clinical problem, and intensive research effort has been devoted to the development of alternative antimicrobial compounds. *S. epidermidis* is an opportunistic pathogen and is the leading cause of chronic or recurrent infections related to the nosocomial or implanted medical devices. AMPs are a unique and diverse group of molecules which are characterized into different subgroups on the basis of their different amino acid composition and structure.

References

- 1 Vuong C, Otto M: *Staphylococcus epidermidis* infections. *Microbes Infect* 2002;4:481–489.
- 2 Prasad S, Nayak N, Satpathy G: Molecular and phenotypic characterization of *Staphylococcus epidermidis* in implant related infections. *Indian J Med Res* 2012;136:483–490.
- 3 Pothitirat W, Chomnawang MT, Gritsanapan W: Anti-acne-inducing bacterial activity of mangosteen fruit rind extracts. *Med Princ Pract* 2010;19:281–286.
- 4 McCann MT, Gilmore BF, Gorman SP: *Staphylococcus epidermidis* device-related infections: pathogenesis and clinical management. *J Pharm Pharmacol* 2008;60:1551–1571.
- 5 Hashemizadeh Z, Bazargani A, Davarpanah MA: Blood culture contamination in a neonatal intensive care unit in Shiraz, Southwest-Central Iran. *Med Princ Pract* 2011;20:133–136.
- 6 Eftekhari F, Mirmohamadi Z: Evaluation of biofilm production by *Staphylococcus epidermidis* isolates from nosocomial infections and skin of healthy volunteers. *Int J Med Med Sci* 2009;1:438–444.
- 7 Ribeiro M, Monteiro FJ, Ferraz MP: Infection of orthopedic implants with emphasis on bacterial adhesion process and techniques used in studying bacterial-material interactions. *Biomater* 2012;2:176–194.
- 8 Otto M: *Staphylococcus epidermidis* – the ‘accidental’ pathogen. *Nat Rev Microbiol* 2009;7:555–567.
- 9 Singh R, Ray P, Das A, et al: Penetration of antibiotics through *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms. *J Antimicrob Chemother* 2010;65:1955–1958.
- 10 Cirioni O, Giacometti A, Ghiselli R, et al: Prophylactic efficacy of topical temporin A and RNAIII-inhibiting peptide in a subcutaneous rat Pouch model of graft infection attributable to staphylococci with intermediate resistance to glycopeptides. *Circulation* 2003;108:767–771.

They are found among all classes of life and represent an important evolutionary component of innate immune response. These peptides have broad-spectrum antibacterial activity and demonstrate potential as novel therapeutic agents.

Natural peptides, their derivatives and de novo-designed AMPs have been reported for their antimicrobial as well as antibiofilm activity against *S. epidermidis*. The mode of action of these peptides may vary and can target bacterial cell membranes by lipid bilayer disruption, interfere with the nucleic acids of the targeted cell or act on the specific YycG/YycF system.

The action of cationic peptides, such as hepcidin and epidermicin, is highly specific for bacterial killing and has not shown any pronounced cytotoxicity on mammalian cells. The synthetic peptides have been designed to include a diverse range of targets showing bactericidal and antibiofilm activity at very low concentrations. Ltx9 is in a phase I clinical trial as a possible candidate against *S. epidermidis* infections. The combination of natural and synthetic peptides with antibiotics has reduced its MIC and lowered the chances for the development of resistant strains.

New advances in technology have directed endeavors towards deciphering the mechanism of action, improving the efficacy and reducing cytotoxicity. However, further efforts are required to address the problems related to bioavailability and large-scale production.

Acknowledgment

We are grateful to the Jaypee Institute of Information Technology, Noida, India, for providing the essential infrastructure facility.

- 11 Balaban N, Stoodley P, Fux CA, et al: Prevention of staphylococcal biofilm-associated infections by the quorum sensing inhibitor RIP. *Clin Orthop Relat Res* 2005;437:48–54.
- 12 Rohde H, Burandt EC, Siemssen N, et al: Polysaccharide intercellular adhesin or protein factors in biofilm accumulation of *Staphylococcus epidermidis* and *Staphylococcus aureus* isolated from prosthetic hip and knee joint infections. *Biomaterials* 2007;28:1711–1720.
- 13 Donelli G, Francolini I, Romoli D, et al: Synergistic activity of dispersin B and cefamandole nafate in inhibition of staphylococcal biofilm growth on polyurethanes. *Antimicrob Agents Chemother* 2007;51:2733–2740.
- 14 Boelens JJ, van der Poll T, Dankert J, et al: Interferon- γ protects against biomaterial-associated *Staphylococcus epidermidis* infection in mice. *J Infect Dis* 2000;181:116771.
- 15 Dunne WM: Bacterial adhesion: seen any good biofilms lately? *Clin Microbiol Rev* 2002;2:155–166.
- 16 Hassan M, Kjos M, Nes IF, et al: Natural antimicrobial peptides from bacteria: characteristics and potential applications to fight against antibiotic resistance. *J Appl Microbiol* 2012;113:723–736.
- 17 Martin E, Ganz T, Lehrer RI: Defensins and other endogenous peptide antibiotics of vertebrates. *J Leukoc Biol* 1995;58:128–136.
- 18 Giuliani A, Pirri G, Nicoletto SF: Antimicrobial peptides: an overview of a promising class of therapeutics. *Cent Eur J Biol* 2007;2:1–33.
- 19 Gordon YJ, Romanowski EG, McDermott AM: A review of antimicrobial peptides and their therapeutic potential as anti-infective drugs. *Curr Eye Res* 2005;30:505–515.
- 20 Pinheiro da Silva F, Machado MC: Antimicrobial peptides: clinical relevance and therapeutic implications. *Peptides* 2012;36:308–314.
- 21 Rahnamaeian M: Antimicrobial peptides: modes of mechanism, modulation of defense responses. *Plant Signal Behav* 2011;6:1325–1332.
- 22 Vizioli J, Salzet M: Antimicrobial peptides from animals: focus on invertebrates. *Trends Pharmacol Sci* 2002;23:494–496.
- 23 Jenssen H, Hamill P, Hancock RE: Peptide antimicrobial agents. *Clin Microbiol Rev* 2006;19:491–511.
- 24 De Smet K, Contreras R: Human antimicrobial peptides: defensins, cathelicidins and histatins. *Biotechnol Lett* 2005;27:1337–1347.
- 25 Lam KLH, Wang H, Siaw TA, et al: Mechanism of structural transformations induced by antimicrobial peptides in lipid membranes. *Biochim Biophys Acta* 2012;818:194–204.
- 26 Oscáriz JC, Pisabarro G: Classification and mode of action of membrane-active bacteriocins produced by Gram-positive bacteria. *Int Microbiol* 2001;4:13–419.
- 27 Marr AK, Gooderham WJ, Hancock RE: Antibacterial peptides for therapeutic use: obstacles and realistic outlook. *Curr Opin Pharmacol* 2006;6:468–472.
- 28 Zasloff M: Antimicrobial peptides of multicellular organisms. *Nature* 2002;415:389–395.
- 29 Park CH, Valore EV, Waring AJ, et al: Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J Biol Chem* 2001;276:7806–7810.
- 30 Barthe C, Hocquellet A, Garbay B: Bacteriostatic activity of the proreagent of human hepcidin. *Protein Pept Lett* 2011;18:36–40.
- 31 Ghiselli R, Giacometti A, Cirioni O, et al: Temporin A as a prophylactic agent against methicillin sodium-susceptible and methicillin sodium-resistant *Staphylococcus epidermidis* vascular graft infection. *J Vasc Surg* 2002;36:1027–1030.
- 32 Capparelli R, De Chiara F, Nocerino N, et al: New perspectives for natural antimicrobial peptides: application as anti-inflammatory drugs in a murine model. *BMC Immunol* 2012;13:61.
- 33 Mangoni ML, Saugar JM, Dellisanti M, et al: Temporins, small antimicrobial peptides with leishmanicidal activity. *J Biol Chem* 2005;280:984–990.
- 34 Conlon JM, Al-Ghaferi N, Abraham B, et al: Strategies for transformation of naturally occurring amphibian antimicrobial peptides into therapeutically valuable anti-infective agents. *Methods* 2007;42:349–357.
- 35 Saviello MR, Malfi S, Campiglia P, et al: New insight into the mechanism of action of the temporin antimicrobial peptides. *Biochemistry* 2010;49:1477–1485.
- 36 Giacometti A, Cirioni O, Ghiselli R, et al: Polycationic peptides as prophylactic agents against methicillin-susceptible or methicillin-resistant *Staphylococcus epidermidis* vascular graft infection. *Antimicrob Agents Chemother* 2000;44:3306–3309.
- 37 Clark DP, Durell S, Maloyll WL, et al: Ranaalexin A novel antimicrobial peptide from bullfrog (*Rana catesbeiana*) skin, structurally related to the bacterial antibiotic, polymyxin. *J Biol Chem* 1994;269:10849–10855.
- 38 Overton IM, Graham S, Gould K, et al: Global network analysis of drug tolerance, mode of action and virulence in methicillin-resistant *S. aureus*. *BMC Syst Biol* 2011;5:68.
- 39 Park CB, Yi KS, Matsuzaki K, et al: Structure-activity analysis of buforin II, a histone H2A-derived antimicrobial peptide: the proline hinge is responsible for the cell-penetrating ability of buforin II. *Proc Natl Acad Sci USA* 2000;97:8245–8250.
- 40 Park CB, Kim HS, Kim SC: Mechanism of action of the antimicrobial peptide buforin II: buforin II kills microorganisms by penetrating the cell membrane and inhibiting cellular functions. *Biochem Biophys Res Commun* 1998;244:253–257.
- 41 Sandiford S, Upton M: Identification, characterization, and recombinant expression of epidermicin NI01, a novel unmodified bacteriocin produced by *Staphylococcus epidermidis* that displays potent activity against *Staphylococci*. *Antimicrob Agents Chemother* 2012;56:1539–1547.
- 42 Kwakman PH, te Velde AA, Vandenbroucke-Grauls CM, et al: Treatment and prevention of *Staphylococcus epidermidis* experimental biomaterial-associated infection by bactericidal peptide 2. *Antimicrob Agents Chemother* 2006;50:3977–3983.
- 43 Qin Z, Lee B, Yang L, et al: Antimicrobial activities of YycG histidine kinase inhibitors against *Staphylococcus epidermidis* biofilms. *FEMS Microbiol Lett* 2007;273:149–156.
- 44 Mechkarska MA, Attoub SB, Sulaiman S, et al: Anti-cancer, immunoregulatory, and antimicrobial activities of the frog skin host-defense peptides pseudohymenochirin-1Pb and pseudohymenochirin-2Pa. *Regul Pept* 2014;194–195:69–76.
- 45 Brancatisano FL, Maisetta G, Di Luca M, et al: Inhibitory effect of the human liver-derived antimicrobial peptide hepcidin 20 on biofilms of polysaccharide intercellular adhesin (PIA)-positive and PIA-negative strains of *Staphylococcus epidermidis*. *Biofouling* 2014;30:435–446.
- 46 Hell E, Giske CG, Nelson A, et al: Human cathelicidin peptide LL-37 inhibits both attachment capability and biofilm formation of *Staphylococcus epidermidis*. *Lett Appl Microbiol* 2010;50:211–215.
- 47 Hell E, Ujvari D, Hultenby K, et al: PS-302 human cathelicidin antimicrobial peptide LL-37 influences *Staphylococcus epidermidis*' biofilm-associated gene-expression and biofilm mass on a medical device surface. *Arch Dis Child* 2014;99:A220–A221.
- 48 Rehman S, Khanum A: Isolation and characterization of peptide (S) from *Pisum sativum* having antimicrobial activity against various bacteria. *Pak J Bot* 2011;43:2971–2978.
- 49 Liu Y, Knapp KM, Yang L, et al: High in vitro antimicrobial activity of β -peptoid-peptide hybrid oligomers against planktonic and biofilm cultures of *Staphylococcus epidermidis*. *Int J Antimicrob Agents* 2013;41:20–27.
- 50 Flemming K, Klingenberg C, Cavanagh JP, et al: High in vitro antimicrobial activity of synthetic antimicrobial peptidomimetics against staphylococcal biofilms. *J Antimicrob Chemother* 2009;3:136–145.
- 51 Dubrac S, Msadek T: Identification of genes controlled by the essential YycG/YycF two-component system of *Staphylococcus aureus*. *J Bacteriol* 2004;186:1175–1181.
- 52 Huang R, Zheng L, Liu H, et al: Thiazolidione derivatives targeting the histidine kinase YycG are effective against both planktonic and biofilm-associated *Staphylococcus epidermidis*. *Acta Pharmacol Sin* 2012;33:8–25.