Protective and Antimicrobial Peptides

Matthew M. Draelos; Zoe Diana Draelos, MD

The common denominator between many dermatologic diseases is infection. Acne represents a *Propionibacterium acnes* infection. Impetigo is a *Staphylococcus aureus* or *Streptococcus* infection. Seborrheic dermatitis is a *Malassezia globosa* fungal infection. Whereas oral and topical antibiotics are the mainstay of acne treatment, it is impossible to eradicate the bacteria because not all organisms are eradicated and recolonization rapidly occurs. Similarly, topical antifungals and antifungal zinc pyrithione shampoos are helpful in the treatment of seborrheic dermatitis, but a cure is not possible. Acne, impetigo, and seborrheic dermatitis are perturbations in the thin film of organisms that coat the skin's surface. Thus, there is a need in dermatology for topical agents that can both eradicate organisms from the biofilm and maintain the health of the biofilm.

Widely used antibiotics, such as methicillin, were used to normalize the biofilm in patients with *S aureus* infections. Methicillin functions by inhibiting bacterial cell wall cross-linkages, thus weakening the cell wall and causing the bacteria to explode. Unfortunately, the emergence of resistant strains of methicillin-resistant *S aureus* (MRSA) has created major epidemiologic problems relevant to dermatology.[1]

Peptides

An area of current research with dermatologic implications is the development of protective peptides. Protective peptides, also known as antimicrobial peptides, are composed of 12 to 50 amino acids and have been isolated from populations as diverse as single-celled organisms, invertebrates, plants, birds, fish, and humans. Such evolutionary conservation testifies to their fundamental importance to survival. Secreted as part of the innate immune system, these antimicrobial peptides play an integral role in the prevention and eradication of infection.[2]

Mr. Draelos is Specialist and Dr. Draelos is Consultant and Researcher, both at Dermatology Consulting Services, High Point, North Carolina.

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One family of bacteriocidal proteins, composed of arginine, lysine, and histidine, has a unique method of irreversibly damaging proteins. Released in an unstructured form, these positively charged antimicrobial peptides fold into their final configuration when attaching to cell membranes to cause membrane disruption, interfere with metabolism, or damage cytoplasmic components. These bacteriocidal proteins offer great promise because resistance is unknown in modern research.[3]

Currently Developed Peptides

Bacteriocins are an example of antimicrobial peptides that are specific for bacterial targets. One well-studied example is mersacidin, which was discovered in 1992 by S. Chatterjee, and is a 4-carbon ring peptide produced by *Bacillus* species strain HIL Y-85,54728 that is active against MRSA and is one of a group of lantibiotics, so named because it contains the rare amino acid lanthionine.[4] Brötz et al[5] developed a recombinant form of mersacidin for clinical use against Gram-positive bacteria, like MRSA, that proved equivalent to the traditional antibiotic vancomycin. Mersacidin kills MRSA by interfering with the synthesis of sugars and amino acids that form the bacterial cell wall, resulting in a breakdown of membrane integrity. This creates channels through which antimicrobial peptides can attack cellular targets, such as organelles in the bacterial nucleus.[6]

Another antimicrobial peptide, CSA-13, showed efficacy in animal studies. Specifically, CSA-13 neutralizes lipoteichoic acid, a bacterial component in the cell wall of Gram-positive bacteria, such as MRSA, responsible for septic-induced organ failure and death. It was found that an injection of CSA-13 produced a statistically significant reduction in sepsis due to lipoteichoic acid neutralizing properties in rats. Although only tested in animals, CSA-13 displays numerous similarities to naturally secreted human antimicrobial peptides.[7]

Antimicrobial Peptides and HIV

In 2003, a US Food and Drug Administration–approved antimicrobial peptide, known as enfuvirtide, was released for human use. Enfuvirtide is a 36-amino acid peptide

structurally similar to a region of the HIV cell envelope. It is similar in function to mersacidin, inhibiting the entry of HIV into the cell, thus preventing infection. Even though it cannot be used as a stand-alone drug, enfuvirtide can be combined with other agents to prevent the human spread of HIV.[8]

Peptide Challenges

While antimicrobial peptides show great promise, several challenges remain. Good anti-infective medications must work efficiently, exhibit low toxicity, remain stable after manufacture, and be reasonably inexpensive. Unfortunately, some synthetic antimicrobial peptides are highly toxic to humans, raising numerous clinical issues. Antimicrobial peptides are also difficult to administer because they must reach the site of infection through the blood stream, which is an extremely slow process. Furthermore, if injected into the bloodstream, the body may inactivate the peptide by breaking down the amino acids en route to the infection. Finally, antimicrobial peptides are expensive to manufacture and cannot be mass-produced like traditional antibiotics. For instance, it is estimated that mersacidin treatment would cost more than $100 per day.[9]

Summary

Bacterial resistance remains a challenging issue for modern medical institutions. The superbug MRSA began as an infection isolated to hospitals and nursing homes, but is now prevalent in communities in the United States and Europe.[10] Will antimicrobial peptides be important in the prevention of resistant organisms? Can antimicrobial peptides be adapted for use in dermatologic biofilm diseases? These are unanswered questions.

The advantage of preventing infection in a safe fashion with limited opportunity for bacterial resistance is tremendous. The development of protective peptides, based on those secreted by most life forms on earth, holds great medical promise.

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