

Preface

Host defense peptides have been studied over several decades. Interest in the application of these agents for therapy is growing. This book surveys our current state of knowledge of host defense peptides and considers their potential for clinical application as well as some of the barriers to this development.

Host defense peptides are part of the innate immune system of multicellular eukaryotes. The range of organisms in which host defense peptides have been discovered is large. These peptides have diverse structures as reviewed in the chapter by Monique van Hoek. These peptides have been most extensively studied as antibacterial agents. They have antimicrobial activity not only in the host in which they are produced, but many of these agents have been shown to be effective when administered to other hosts. In this chapter some of the unanswered questions and ongoing areas of development are highlighted in boxes inserted in the text. The activity of many of these agents is not limited to bacteria, but as reviewed by Lohner and Leber, some of these agents are antifungal. The structure and chemical composition of fungi are more similar to mammalian cells than they are to bacteria. Nevertheless, differences exist in fungi that can be exploited for developing antifungal agents. These include the nature of their cell wall, the structure of their membrane sterol, ergosterol that is different from cholesterol, as well as the chemical structure of fungal sphingosine. Host defense peptides can also be immunomodulatory and inflammo-modulatory. It is therefore not surprising that these agents can also have antiviral activity. The antiviral activity of host defense peptides is reviewed by Sousa, Casanova, Stevens, and Barlow. In addition to their stimulation of inflammation and the immune system, these antiviral host defense peptides can also directly affect viral particles and have broad spectrum antiviral activity. The mechanism of action of some of these agents is summarized in a table and the therapeutic potential of the host defense peptides as antiviral agents is discussed. A very different application of host defense peptides is discussed by Gaspar and Castanho, regarding their use in cancer therapy. There is evidence

suggesting this as a possible application of these agents, but it is suggested that further development of the application of host defense peptides in this area will require a more complete understanding of their mechanism of anticancer action. An application of host defense peptides not often discussed is that of plant host defense peptides and their possible application in agriculture. Goyal and Mattoo review this field and show that host defense peptides from plants are structurally diverse and have a variety of mechanisms of action, including damaging the cell membrane as well as having intracellular targets.

One of the properties of host defense peptides is that they indirectly protect against pathogens by mechanisms involving inflammation and immunity. Eicosanoids play an important role in regulating innate immunity and host defense. One source of the interaction is from the influence of eicosanoids and of arachidonic acid in the expression of host defense peptides. In addition, some host defense peptides stimulate the synthesis of eicosanoids, which themselves are immunomodulatory. The relationship between host defense peptides and eicosanoids is outlined in the chapter by Wan, Tang, and Haeggström.

One of the reasons that there is an immediate need to develop novel and potent host defense peptides is that many organisms are developing resistance to traditional antibiotics. It had been initially thought that since antimicrobial peptides have been effective throughout evolution it would be less likely that resistance would develop. In addition, many of these agents act at the level of the membrane of the pathogen, giving less opportunity for the development of altered metabolic or genetic properties of the pathogen. However, over time resistance has developed to virtually every antibiotic. In long term, it might require something like multidrug evolution strategies to reverse antibiotic resistance (Baym et al. 2016). However, until such strategies become developed, drugs to inhibit resistance mechanism may provide an interim solution, as described by Phoenix, Dennison, and Harris. There is also a family of compounds that has been used in conjunction with traditional antibiotics to reverse multidrug resistance in bacteria. These agents are oligomers of acyl-lysines that are described in the review by Mor. These compounds can also be linked to insoluble resins for the removal and detection of bacteria.

While there is a large variety of chemical structures and mechanisms of action of natural host defense peptides, none of them have properties to make them ideally suited for therapeutic application. There have thus been efforts, such as those described by Mor, to design novel agents. In addition to novel compounds like the oligo-acyl-lysines, efforts are being made to utilize the common features of host defense peptides. Wang describes the development of an algorithm to reveal the features that are common among host defense peptides from a wide range of organisms. He suggests that there are two alternative paths that can be used to optimize the properties of the designed peptide. One is by a combinatorial synthesis and drug screening. The other is by structure-based rational drug design. The two methods are not mutually exclusive, but can be used in combination. In the next

article, Deshayes, Lee, Schmidt, Xian, Kasko, and Wong present the dilemma that most antimicrobial peptides are both non-specific and toxic to the host and are of low potency against pathogens, requiring the use of high concentrations. However, the alternative is the use of antibiotics that are highly potent and specific but against which the resistance easily develops. This chapter suggests that hybrid molecules can be designed to combine the best features of non-specific antimicrobial peptides with the high potency of antibiotics. Additionally, the drug can be made resistant to proteolytic degradation by using β -peptide linkages.

The final section discusses the perspectives for a more widespread clinical use of host defense peptides. The role of bacterial infection as a contributor to preterm birth in humans is discussed in the chapter by James and Bajaj-Elliott. Among the host defense mechanisms are the actions of host defense peptides. Mansour, Hancock, and Otto focus their discussion specifically on the treatment of infections by *Staphylococcus aureus*. This is the most abundant bacteria in the microbiome of the skin. This bacteria has developed resistance to almost all known antibiotics. Infections with methicillin-resistant *Staphylococcus aureus* (MRSA) have claimed more lives than HIV/AIDS. Challenges to the development of therapies based on the use of host defense peptides include the low potency and the weak specificity of these agents, thus creating a narrow therapeutic window. Host defense peptides have a short half-life in the body, largely as a result of proteolytic degradation, thus limiting their efficacy. Another difficulty with the clinical use of host defense peptides is that they are immunogenic. Thus, these peptides have a dual role in stimulating the immune system. On the one hand, this property increases their effectiveness against the invading pathogens; on the other hand, the host defense peptide itself can become an immunogen, especially because its low potency requires that it be used at high concentrations. This antigenicity reduces the effectiveness of these peptides and can even lead to cross-reaction with endogenous proteins, resulting in autoimmune diseases. Another limitation for the commercialization of host defense peptides as drugs is the high cost of production of peptide synthesis. This could be ameliorated with the use of shorter peptides or non-peptide drugs. Further improvements could include synergistic cocktails, stimulation of endogenous production of host defense peptides, and using drugs to overcome resistance mechanisms.

There has been much progress in the identification of host defense peptides in a large number of organisms. Attempts have been made in developing host defense peptides for diverse applications including in the field of urology for the use in removing kidney stones; as stimulants of insulin release with potential for type II diabetes therapy; as useful agents in lung infections; as coatings for implanted devices such as catheters and other applications. The mechanism of action of host defense peptides is varied but in general these compounds tend to be non-specific and do not have very high potency. They also stimulate resistance mechanisms.

Nevertheless, currently many efforts are made to overcome these limitations and there is hope that we are at the beginning of a new period in which host defense peptides will be developed for a variety of therapeutic applications.

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Reference

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