DEVELOPMENT OF ANTIMICROBIAL PEPTIDES AS THERAPEUTIC AGENTS

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1 INTRODUCTION

1.1 Resistance to Classical Antibiotics

The great success of the pharmaceutical industry in creating new antibiotics over the past four decades has perhaps caused the general public and portions of the scientific community to become complacent about the potential for bacterial resistance. Indeed, antibiotic resistance due to the extensive clinical use of classical antibiotics has become a great concern in recent years to medical practitioners and scientists in the field of infectious disease. For instance, over the past 5 years, the rate of resistance to penicillin and cefotaxime has increased by more than 300 and 1000%, respectively (Fig. 1; http://www.cdc.gov/drugresistance/community/files/ads/resis_an.htm). Classical antibiotics work by inhibiting bacterial cell wall synthesis, protein synthesis, DNA (deoxyribonucleic acid) replication, or by modifying metabolism. Bacteria can resist antibiotics as a result of chromosomal changes (mutation or inductive expression of a latent chromosomal gene) or the exchange of genetic material via plasmids and transposons [1]. Antibiotics are rendered inactive by three major mechanisms: (1) antibiotic inactivation by destruction or modification, (2) prevention of access of the antibiotic to the target, and (3) alteration of the target site of the antibiotic [2]. Bacteria have a remarkable ability to overcome each new reagent synthesized as a potential classical antibiotic. Consequently, the current priority is the development of alternative drugs and/or the isolation of native molecules that would allow the consistent and proper control of pathogen-caused diseases [3]. Ideally, these molecules should be active over a wide range of pathogens, easily produced, and not prone to induce resistance.

1.2 Antimicrobial Peptides (AMPs) as Antibiotics

Clearly, the development of a new class of antibiotics with very different modes of action compared to classical antibiotics is urgently required. AMPs have emerged as promising candidates for such required novel therapeutic agents. Although the exact mode of action of AMPs has not been established, it is generally accepted that the cytoplasmic membrane is the main target of many AMPs, whereby peptide accumulation in the membrane causes increased permeability and a loss of barrier function, resulting in the leakage of cytoplasmic components and cell death. The development of resistance to membrane-active peptides whose sole target is the cytoplasmic membrane is thought to be considerably reduced compared with that of many current antibiotics, which have more specific molecular targets [4]. This prediction has been substantiated in several studies [5–7]. However, the major barrier to the use of AMPs as antibiotics is their toxicity or ability to lyse eukaryotic

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