Research Advances in the Development of Peptide Antibiotics

LISA M. ROSSI,[1] PRIYA RANGASAMY,[1] JIE ZHANG,[2] XIAO-QING QIU,[2] GEORGE Y. WU[1]

[1]Division of Gastroenterology-Hepatology, University of Connecticut Health Center, 263 Farmington Ave, Farmington, Connecticut

[2]Key Laboratory of Transplant Engineering and Immunology, Ministry of Health, West China Hospital, Sichuan University, Chengdu, The People's Republic of China

Received 13 September 2006; accepted 20 April 2007

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21053

ABSTRACT: Bacterial resistance to antibiotics is a growing concern in both nosocomial and community acquired infections. Resistance began to emerge as early as the 1950s. Much research has been dedicated to the improvement of existing classes of antibiotics. Antimicrobial peptides (AMPs) are part of the innate immune system, and an important component of immune defense. They are produced by plants, animals, insects, and single celled organisms, and possess anti-microbial properties. As such, they are an ideal target for future antibiotic production. Bacteriocins are a subgroup of AMPs, produced by various bacteria. It has been shown that the production of chimeric peptides consisting of bacteriocins and pheromones can be targeted toward the killing of specific bacterial species. In contrast to the clonal, acquired adaptive immunity, endogenous peptide antibiotics provide a fast and energy-effective mechanism as front line defense. This review will provide an overview of AMPs and their potential for target-specific anti-infective therapy. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:1060–1070, 2008

Keywords: peptides; antiinfectives; biomimetics; biotechnology; cell biology; cell culture; drug resistance

INTRODUCTION

Antimicrobial peptides (AMPs) are effector molecules of the innate immune system.[1] They are present throughout nature and produced by plants, animals, and some single celled organisms.[2] They possess direct antimicrobial function, as well as the ability to act as mediators of inflammation. More than 700 AMPs have been described.[1] Bacterial AMPs can be classified based on whether they are ribosomally or non-ribosomally synthesized.[1] Table 1 details several classes of AMPS which will be discussed in this review. To inhibit bacteria and other microbes, mammals produce an array of molecules which can be divided roughly into antimicrobial proteins and inorganic disinfectants such as nitric oxide and hydrogen peroxide.[3] In humans, peptide antibiotics of three families have been identified: defensins, cathelicidins, and histatins.[4] In addition to defensins and cathelicidins, a number of other proteins with antimicrobial activity have been identified in the intestine. These include ubiquicidin, ribosomal proteins L30, L39, and S19, histones H1.5 and H2B, phospholipase A2,

Correspondence to: George Y. Wu (Telephone: 860-679-3158; Fax: 860-679-3159; E-mail: wu@nso.uchc.edu)

Journal of Pharmaceutical Sciences, Vol. 97, 1060–1070 (2008)

Table 1. Classification of Antimicrobial Peptides

Origin	Class	Sub-Type	Structural Characteristics	Example	Source
Bacterial	Bacteriocin[1,6]	Lantibiotics (types A and B)	A—elongated, cationic B—globular	Nisin	Lactic acid producing bacteria
Bacterial	Bacteriocin[9]	Colicin	α-helices	Colicin 1a	*E. coli*
Fungus	Defensin[18]		α-helix, 2 anti-parallel β-sheets	Plectasin	Pseudoplectania nigrella
Insect	Defensin[31,35,36]		Linear sequence, 37 residues	Cecropin A Mellitin	Many insect species
Vertebrate (including human)	Defensin[1,4]	α-defensin	29–35 aa Triple strand β-sheet, β-hairpin	Human neutrophil peptides (HNP) 1–4 Human defensins (HD) 5–6	
Vertebrate (including human)		β-defensin	36–42 aa 6 cysteines, disulfide bridges	Human B-defensin (hBD) 1–4 Tracheal antimicrobial peptide (TAP)	Human Cow
Vertebrate (including human)		Θ-defensin	Circular molecular structure	Rhesus theta-defensin 1 (rTH-1)	Rhesus monkey
Mammalian	Cathelicidin[1,4]		Pro-peptidet Highly conserved 100 aa residue domain Product 12–80 residues α-helical or β-sheet	LL-37 0r hCAP-18 CRAMP rCRAMP Protegrin, PMAP-23, PR-39 rhLL-37, RL-37 CAP-18 SMAP29, SMAP 34 BMAP-28[28]	Human myeloid cells Mouse Rat Pig Monkey Rabbit Sheep Cattle
Human	Granulysin[1]		Related to saposin, small lip-associated CNS proteins		Human cytolytic T lymphocytes
Human	Histatins[4]		Histidine rich polypeptides		Human saliva
Human	Thrombocidin[5]		Variants of CXC chemokines, differing from these chemokines by a C-terminal truncation of 2 amino acids	TC-1, TC-2	Human platelets
Human	Others[3]			Ubiquicidin Ribosomal proteins L30, 39, S19 Histones H1.5, H2B Phospholipase A2 Eosinophilic cationic protein 15-mer dermaseptin[32] G10KHC (STAMP)[29]	

DOI 10.1002/jps