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BACTERIOCIN: AN ALTERNATIVE TO ANTIBIOTICS

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ABSTRACT

Bacteriocins are ribosomally synthesized antimicrobial peptides produced by microorganisms belonging to different eubacterial taxonomic branches. Most of them are small cationic membrane-active compounds that form pores in the target cells, disrupting membrane potentials and causing cell death. The production of small cationic peptides with antibacterial activity is a defense strategy found not only in bacteria, but also in plants and animals. There are a wide variety of bacteriocins produced by different bacterial genera that must be further studied. As bacteriocins have been thought as alternative bioactive substances to avoid the broad side-effects and alarming resistance dissemination produced by the use of classical antibiotics. The incorporation of bacteriocins as bioactive compounds in a pharmaceutical product needs different type of studies to demonstrate the no existence of adverse effects, which must be performed both in in vitro and in in-vivo experimental systems. Up today, the use of bacteriocins as bioactive compounds into pharmaceutical products for human use has not been accepted yet by the regulators or reference organizations. Bacteriocins are classified according to different criteria by different authors; in this review, we will summarize the principal of bacteriocin classifications, highlight their main physical and chemical characteristics, and discuss their application as an alternative to antibiotics.

KEYWORDS: Bacteriocin, Alleopathy,Probiotic, antibiotics, resistance.

INTRODUCTION

Allelopathy is the production of chemical compounds which are toxic to other organisms but not to the producers of these compounds. For microorganisms, there is wealth of data

demonstrating that allelopathy is an important mediator of intra- and inter-specific interaction consequently a significant factor in maintaining microbial biodiversity.[1] In bacteria these allelopathic substances include metabolic byproducts such as bacteriocins.Bacteriocins are found in almost every bacterial species examined to date, and within a species tens or even hundreds of different kinds of bacteriocins are produced.[2] These are ribosomally synthesized antimicrobial peptides produced by microoorganisms belonging to different eubacterial taxonomic branches.[3] The production of small antibiotic peptides is a common defense strategy against bacteria that is displayed not only by microorganisms, but also with by animals and plants. Maganins, cecropins and defensins are animal[4,5] and thionins are plant antimicrobial peptides.[6] Halobacteria universally produce their own version of bacteriocins, the halocins.[7] Streptomycetes commonly produce broad-spectrum antibiotics. The killing ability of bacteriocins is considered a successful strategy for maintaining population and reducing the numbers of competitors to obtain more nutrients and living space in environments. Unlike most antibiotics, which are secondary metabolites, bacteriocins are ribosomally synthesized and sensitive to proteases while generally harmless to the human body and the surrounding environment.To maintain their existence or ecological niche,many species have developed systems of antimicrobial defense against competitors or infections.[8] Table1 provides examples of many antimicrobial peptides produced by eukaryotic organisms. Sometimes the peptides act against a specific group of competing organisms; sometimes their broad spectrum of activity serves as a more general defense mechanism. Antimicrobial peptides protect the host by different mechanisms, but most commonly by permeabilizing the target cell membrane, an irreversible leakage of cellular material and consequently cell death.

This review focuses on the classification of bacteriocins from Gram-negative and Gram-positive bacteria its nature, mode of action and the application of bacteriocin as an alternative to antibiotics.

THE BIOLOGY OF BACTERIOCINS

Bacteriocins were first identified almost 100 years ago as a heat-labile product present in cultures of *Escherichia coli* V and toxic to *E. coli* S and were given the name of colicin to identify the producing species.[9] Frederick demonstrated that collisions were proteins and that they had a limited range of activity due to the presence or absence of specific receptors on the surface of sensitive cells.[10] Since then, bacteriocins have been found in all major lineages of Bacteria and, more recently, have been described as universally produced by

some members of the Archaea.[11] According to Klaenhammer, 99% of all bacteria may make at least one bacteriocin, and the only reason we have not isolated more is that few researchers have looked for them.

Two main features distinguish the majority of bacteriocins from classical antibiotics: bacteriocins are ribosomally synthesized and have a relatively narrow killing spectrum.[12] The bacteriocin family includes a diversity of proteins in terms of size, microbial target, mode of action, release, and immunity mechanisms and can be divided into two main groups: those produced by Gram-negative and Gram-positive bacteria.

CLASSIFICATION OF BACTERIOCIN

Bacteriocins are categorized in several ways, including producing strain, common resistance mechanisms, and mechanism of killing. There are several large categories of bacteriocin which are only phenomenologically related. These include the bacteriocins from gram-positive bacteria, the colicins [13] the microcins, and the bacteriocins from Archaea. The bacteriocins from E. coli are called colicins (formerly called 'colicines,' meaning 'coli killers'). They are the longest studied bacteriocins. They are a diverse group of bacteriocins and do not include all the bacteriocins produced by E. coli. For example the bacteriocins produced by *Staphylococcus warneri* are called as warnerin[14] or warnericin. In fact, one of the oldest known so-called colicins was called colicin V and is now known as microcin V. It is much smaller and produced and secreted in a different manner than the classic colicins. The bacteriocins of lactic acid-fermenting bacteria are called lantibiotics.[15] Several classification criteria have been used to classify the bacteriocins produced by bacteria.[16] Table 2 summarize the features of various bacteriocins.

BACTERIOCINS OF GRAM-NEGATIVE BACTERIA

Recent surveys of *E. coli*, *Salmonella enterica*, *Hafnia alvei*, *Citrobacter freundii*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* reveal levels of bacteriocin production ranging from 3 to 26% of environmental isolates.[18,19] Colicins, bacteriocins produced by *E. coli*, are found in 30–50% of the strains isolated from human hosts and are often referred to as virulence factors Much higher levels of bacteriocin production have been found in some Gram-negative bacteria, such as *Pseudomonas aeruginosa*, in which >90% of both environmental and clinical isolates produce bacteriocins.[20]

Since their discovery, the colicins of *E. coli* have been the most extensively studied Gram-negative bacteriocins, and they now serve as a model system for investigating the mechanisms of bacteriocin structure/function, genetic organization, ecology, and evolution. Colicins are high molecular weight proteins that kill target cells through a variety of mechanisms.Nomura showed that colicins E1 and K inhibit macromolecular synthesis without arrest of respiration, colicin E2 causes DNA breakdown, and colicin E3 stops protein synthesis.[21] In each case, he showed that the lethal action is reversed by treatment with trypsin. Since his pioneering work, colicins were shown to kill their targets by either membrane permeabilization or nucleic acid degradation.[22,23]

Colicins are usually encoded on one of two types of colicinogenic plasmids.[24] Type A plasmids are small (6 to 10 kb) and present in numerous copies per cell. They are mobilizable in the presence of a conjugative plasmid and are amplifiable. Type B are monocopy plasmids of about 40 kb, which carry numerous genes in addition to those encoding colicin activity and are able to conjugate. However, plasmid carriage of bacteriocins is not a requirement.

A colicin protein is comprised of three functionally distinct domains; receptor recognition, protein translocation, and killing.[25] In colicins, the central domain comprises about 50% of the protein and is involved in the recognition of specific cell surface receptors on the outer membrane of the target cell.[26] The N-terminal domain (<25% of the protein) is responsible for translocation of the protein through the cell envelope by either the Tol or Ton machinery to its target.[27] In addition to colicins, *E. coli* strains produce a second type of bacteriocin, known as microcins, which are smaller than colicins and share more properties with the bacteriocins produced by Gram-positive bacteria, including thermostability, resistance to some proteases, relative hydrophobicity, and resistance to extreme pH.[28-31]

The successful use of probiotics-producing colicins, microcins, or any other bacteriocins requires understanding the factors influencing the frequency of bacteriocin production in a bacterial population. This aspect of bacteriocin ecology was recently studied in clinical and environmental *E. coli* populations. Recent evidence indicates that the frequency of bacteriocin production in *E. coli* populations can vary from 10 to 80% depending on the animal host from which they were isolated.[32-34]

BACTERIOCINS FROM GRAM-POSITIVE BACTERIA

Unlike colicins from Gram-negative bacteria, which are plasmid or chromosome encoded 25–80 kDa proteins, the Gram-positive bacteria bacteriocins exert similar characteristics to microsins. In Gram-positive bacteria, lactic acid bacteria (LAB) are the typical bacteria producing a variety of bacteriocins of different sizes, structures, physicochemical properties, and inhibitory spectrum.[35-38] Due to the large diversity of bacteriocins are generally divided into class I (modified peptides, lantibiotics), class II (unmodified peptides, non-lanthionine), and class III (large proteins, heat unstable) (Table 3).

MODE OF ACTION

A widely accepted hypothesis for the mode of action of bacteriocins is that the bacteriocin acts in two steps, involving adsorption of the bacteriocin to specific or nonspecific receptors on the cell surface resulting in cell death.[39] Several other general observations may be made which apply to the antibacterial activities of the low-molecular-weight bacteriocins: (i) within a given species, some strains may be sensitive and others may be resistant to a particular bacteriocin; (ii) a strain that appears to be sensitive to a bacteriocin may also have some cells in the population that are resistant to it; (iii) a strain can be sensitive to one bacteriocin while being resistant to a similar type of bacteriocin; (iv) cells of a strain producing one bacteriocin can besensitive to another bacteriocin;(v) although the spores of a strain whose cells are sensitive to a bacteriocin are resistant to that bacteriocin, they become sensitive following germination; (vi) under normal conditions, gram-negative bacteria are not sensitive to bacteriocins produced by gram-positive bacteria.[40]

RESISTANCE AND IMMUNITY TO BACTERIOCIN

Most bacteriocins kill target cells by permeabilization of the cell membrane, and the activity is often very specific, since they employ specific receptors on the target cell surfaces. The target receptors of a few bacteriocins have been identified. For example, nisin and a number of other lantibiotic bacteriocins (peptides containing posttranslationally modified residues) use the cell wall precursor lipid II as a docking molecule on target cells.[41,42] Furthermore, it has been shown in recent years that a set of bacteriocins produced by both Gram-positive and Gram-negative species can employ the membrane components of the mannose phosphotransferase system (Man-PTS) on sensitive cells as receptor molecules. These bacteriocins include the pediocin-like bacteriocins.[43,44] The lactococcal bacteriocins

lactococcin A and B.[45] and microcin E492 from *Klebsiella*, which can target Man-PTS in the inner membrane of *Escherichia coli*.[46]

BACTERIOCIN APPLICATIONS

The rapid rise and spread of multi-resistant bacterial pathogens have forced the consideration of alternative methods of combating infection.[47] One of the limitations of using broad-spectrum antibiotics is that they kill almost any bacterial species not specifically resistant to the drug. Given such a broad killing spectrum,these antibiotics are used frequently, which results inan intensive selection pressure for the evolution of antibiotic resistance in both pathogen and commensal bacteria.[48] Current solutions to this dilemma involve developing a more rationale approach to antibiotic use, which involves curtailing the prescription of drugs for anything other than bacterial infections, cycling through different drugs over a shorter time frame, and educating the public about the necessity of taking an entire course of antibiotics.[49] Bacteriocins provide an alternative solution. With their relatively narrowspectrum of killing activity, they can be considered "designer drugs,"which target specific bacterial pathogens. Given the diversity of bacteriocins produced in nature, it is a relatively simple task to find bacteriocins active against specific human pathogens.

Table 1: Antimicrobial peptides of eukaryotic origin.

Antimicrobial peptide	Source	Mode of Action	Antimicrobial Spectrum	Toxicity	References
Pardaxin	*Pardachiros maroratus (*RedSea. Sea Moses Sole) and *Parpaooninus* Žpeacock sole.	Forms barrel stave pores which induce release of neurotransmitters	Gram +,more effective againsty Gr-	Reduced Hemolysis against human rbc	Oren and Shai, 1996[12]
Melittin	Bee venom	a helix inserts in membrane	Gr+ and Gr-	Lyse mammalian and bacterial cells	Oren and Shai, 1996[12],
Ceratotoxin	*Ceratitis capita*	Unknown	Gr+ and Gr-	Lytic to *E. coli* K-12	Marri et al., 1996[13]
Histatins	Human saliva	Form pores in membranes	Broad spectrum,bacteria and fungi	Little or none	Helmerhorst et a.,1997[14]
Trichorzins	*Trichoderma* (soil fungi)	Forms voltage gated ion channels	S.aureus but not E.coli	Hemolytic	Goulard et al., 1995[15]
Cecropins	Humoral immune system of some insects, i.e., *Hyalo*phora *cecropia* (giant silk	Disrupts lipid bilayer of membrane	Gr- more sensitive than Gr+	Lyse anionic liposomes and bacteria	Moore et al., 1996; Hansen, 1993;Helmerhorst et al.,1997; Boman, 1991[16,17,14,18]

	moth)				
Magainins	Frogs and other amphibians, i.e., *Xenopus laeÕis*	Forms anion permeable channels in membrane	Bacteria and Fungi	Lytic	Higazi et al., 1996;Helmerhorst et al.,1997; Hansen,1993.[19,14,17]
Defensins	Mammalian neutrophils	Form voltage gated channels	Gr+ ,Gr-,fungi, enveloped viruses	Cytotoxic	Higazi et al., 1996;Kagan et al., 1994[20]

Table 2: Classification of bacteriocins adapted from Klaenhammer 1993.[14]

Group	Features	Bacteriocins (group representatives)
I Ia	Lantibiotics, smallŽ-5 kDa.peptides containing lanthionine and b-methyl lanthionine	Nisin
Ib	Globular peptides with no net charge or net negative charge	Mersacidin
II	Small heat-stable peptides, synthesized in a form of	Pediocin PA-1, sakacins A and P leucocin A, carnobacteriocins, etc. Lactococcins G and F, lactacin F Plantaricin EF and JK Helveticins J and V-1829, acidophilucin A, lactacins A and B
IIa	Precursor which is processed after two glycine residues, active against *Listeria*, have a consensus sequence of YGNGV-C in the N-terminal	
IIb	Two components systems: two different peptides required to an active portion complex	
III	Large molecules sensitive to heat	

Table 3: Properties of bacteriocin obtained from different sources.

Classification/features	Bacteriocins	Molecular weight (Da)	Producing strain	References
CLASS I				
The bacteriocins are post-translationally modified, linear or globular peptides containing lanthionine, β-methyl lanthionine and dehydrated amino acids	Nisin A	3352	*Lactococcus lactis subsp. lactic*	Field et al., 2012
	Nisin U	3029	*Streptococcus uberis*	Wirawan et al., 2006
	Nisin Z	3493	*Lactococcus lactis subsp. lactic*	Mulders et al., 1991
	Mersacidin	1824	*Bacillus sp.Y85,54728*	Chatterjee et al., 1992
	Labyrinthopeptin A2	1922	*Actinomadura sp.*	Meindl et al., 2010
	subtilosin A	3399	*Bacillus subtilis* 168	Babasaki et al., 1985
CLASS II				
Heat stable, unmodified, non-lanthionine-containing bacteriocins, heterogeneous class of small peptides				
Class IIa (pediocin PA-1like bacteriocins)	pediocin PA-1	4629	*Pediococcus acidilactici* PAC-1.0	Henderson et al., 1992
	carnobacteriocin X	3602	*Carnobacterium maltaromaticum* C2	Tulini et al., 2014
Class IIb (composed of two peptides)	lactacin F	4755	*Lactobacillus spp.*	Fremaux et al., 1993
	ABP-118	4096	*Lactobacillus salivarius subsp. salivarius* UCC118	Flynn et al., 2002
Class IIc (circular peptide)	carnocyclin A	5862	*Carnobacterium maltaromaticum* UAL307	Martin-Visscher et al., 2008
	enterocin AS-48	7149	*Enterococcus faecalis*	Samyn et al., 1994
Class IId (linear, non-pediocin like, single-peptide)	epidermicin NI01	6074	*Staphylococcus epidermidis*	Sandiford and Upton, 2012
	lactococcin A	5778	*Lactococcus lactis subsp. Cremoris*	Holo et al., 1991
CLASS III				
Large, heat unstable proteins	Caseicin 80	~42000	*Lactobacillus casei* B80	Muller and Radler, 1993
	Enterolisin A	34501	*Enterococcus faecalis* LMG 2333	Nilsen et al., 2003
	Helveticin J	37511	*Lactobacillus helveticus* 481	Joerger and Klaenhammer, 1990

CONCLUSION

The effectiveness of bacteriocins as food preservatives is well demonstrated. Though nisin is the only purified bacteriocin used commercially, others such as pediocin, have application in food systems.Though bacteriocins are inhibitory against foodborne pathogens such as *L. monocytogenes*, they are not antibiotics. Their synthesis and mode of action distinguish them from clinical antibiotics. Additionally, organisms that show resistance to antibiotics are generally not cross-resistant with bacteriocins, and unlike antibiotic resistance, bacteriocin resistance is not usually genetically determined. Hence bacteriocin could be considered as a potential alternative to antibiotics.

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