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Review

Bacteriocins of Gram-positive bacteria: Features and biotherapeutic approach

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Bacteriocins are potent antimicrobial peptides produced by every bacterial and archeal species reported to date. The most studied are bacteriocins produced by lactic acid bacteria (LAB) and many species of *Bacillus*. Knowledge on the classification, biosynthesis and transport of these peptides is changing continually because the discovery and characterization of new bacteriocins increases, thus, the research reports increase at the same rate. The bacteriocins are considered the most promising molecules with enormous possibilities and realities for the design of improved antibiotics possessing specific characteristics, mostly against antibiotic resistant bacteria. Here, current information on the generalities, classification proposals, biosynthesis and transport systems involved in the bacteriocins secretion is review. Finally, this review will focus on the new approaches for its application in veterinary medicine and human health.

Key words: Bacteriocin, biotherapeutic, resistant bacteria, human health.

INTRODUCTION

Bacteriocins are antimicrobial protein produced by all major lineages of bacteria and archeal species studied to date. Technically are defined as antimicrobial peptides ribosomally synthesized, which may or may not be post-translationally modified and its spectrum of action. Bacteriocins produced by lactic acid bacteria (LAB) are the most studied, however, there are also species of *Bacillus*, Gram-positive aerobic organism that can resist environmental stress by forming endospores (Kumar et al., 2011), and also, is capable of producing significant quantities of powerful bacteriocins (Abriouel et al., 2011).

Characteristics of bacteriocins from Gram-positive bacteria are very well known, such as the synthesis regulated by particular systems for each bacteriocins class. The synthesis is not lethal to the producer cell due to the transport generally is mediated by inner transport systems like the Sec System and the ABC-transporter System (Gutiérrez et al., 2006). Also has been reported

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extensively its spectrum of antimicrobial action, including both narrow spectrum with limited activity and primarily only useful against related species of microorganisms, and broad spectrum active against both Gram-positive and Gram-negative organisms and some fungi (Salazar-Marroquín et al., 2016).

CLASSIFICATION APPROACH OF BACTERIOCINS

In recent years, there has been booming research on bacteriocins, and their classification by size, spectrum of activity, mode of action, chemical composition, stability, biosynthesis and other factors. Actually, the more inclusive classification of these widely heterogeneous peptides considers all the above points, subdivided into classes including the subclasses previously reported for unmodified bacteriocins synthesized by LAB (Cotter et al., 2013).

Class I: Lantibiotics. Small peptides less than 5 kDa, active at membrane level and containing some unusual amino acids such as lanthionine, β-methyl-lanthionine and deshirdro alanine formed due to subsequent modifications to the process of translation. The formation of uncommon amino acids is explained by dehydration of the amino acids serine and threonine, with the subsequent addition of sulfur of cysteine and the formation of dehydroamino double bonds (Chen and Hoover, 2003). Class I is subdivided according to its antimicrobial activity and chemical structure into two types A and B (Cotter et al., 2005).

Class I A: Positively charged elongated peptides that act at the level of the bacterial membrane forming pores, promoting the dissipation of the membrane potential and lacking in small metabolites of sensitive cells.

Class I B: Negatively charged small globular peptides, the antimicrobial activity of these is linked to the inhibition of specific enzymes.

Class II: No lantibiotics. Peptides less than 10 kDa in molecular weight, thermostable, do not undergo posttranslational modifications. Three classes are released from this group, shown below.

Class IIa: Active peptides against *Listeria* sp. contain a consensus sequence in the N-terminal region - TGNGVXC.

Class II b: Complex of two peptides necessary for better antimicrobial activity consisting in pore formation.

Class II c: Small peptides, thermoset, unmodified, which are transported by a leader peptide.

Class II d: Novel leaderless bacteriocins, atypical in the sense that they are synthesized without an N-terminal leader sequence and with unique biosynthetic mechanisms (Oman and van der Donk, 2010).

Class III: Bacteriolicinas, with a molecular weight greater than 30 kDa, are thermolabile and its action consist of the hydrolysis of the cell wall of sensitive bacteria.

Clas IV: Circular bacteriocins. Peptides covalently linked head to tail and share a common structural motif (Martin-Visscher et al., 2009). The common motif has four or five conserved α helices enclosing a compact hydrophobic core. The most studied circular bacteriocin is enterocin AS-48 from *Enterococcus faecalis*. Others circular bacteriocins are butyrivbriocin AR10, gassericin A, circularin A, subtilosin A, uberloysin, reutericin and lactocyclicin Q (Nes et al., 2007)

BACTERIOCIN BIOSYNTHESIS

Commonly bacteriocins are synthesized in a particular way as an inactive peptide with an N-terminal leader attached to a C-terminal called pre-peptide or rather that pre-bacteriocin. The pathway includes the pre-bacteriocin production, some reactions of particular modification and late the cleavage of the leader peptide and then, the translocation of the pro-bacteriocin across the cell membrane.

Bacteriocins genetic determinants encoding for the synthesis of bacteriocins are grouped in one or two operons consisting of different components, located on plasmids, in the chromosome, or in transposons inserted in the chromosome (Drider et al., 2006; Wirawan et al., 2007). The components includes:

1) The structural gene, encodes the pre-probacteriocin, containing an N-terminal, the leader sequence double-glycine type or peptide signal type sequences type. Double-glycine-type leader is characterized by two conserved glycines at its C-terminus, recognized by ABC transporters for processing the leader sequence and secretion of the mature bacteriocin to the extracellular medium.

The signal peptide type sequences (SP) enable the processing and secretion of bacteriocins through the general transport path (GSP) (Driessen and Nouwen, 2008).

2) Immunity gene, encodes small proteins, with sizes of approximately 51 to 154 amino acids, which protects the producing strain of the bacteriocin itself.

3) Genes encoding proteins responsible for processing, transport and secretion of the pre-probacteriocin.

4) Genes encoding the enzymes responsible for post-translational modifications of the probacteriocin.

5) Genes encoding components involved in the regulation of the synthesis. The production of bacteriocins is considered an adaptive response and therefore, is

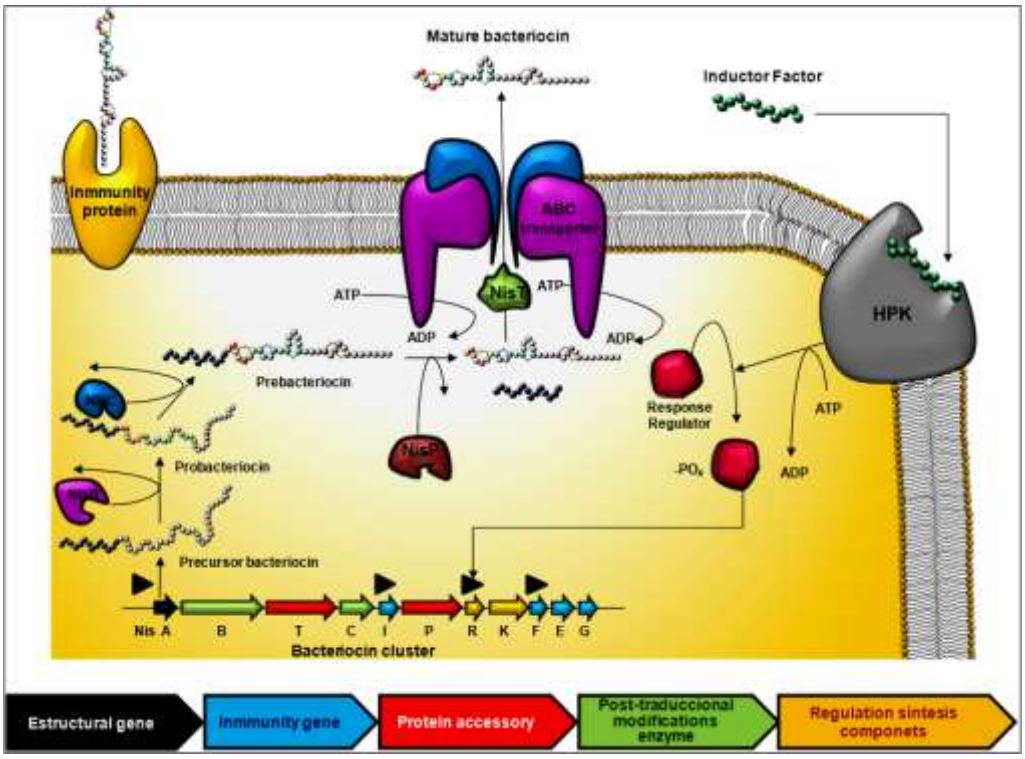

Figure 1. Genetic determinants encoding for the synthesis of bacteriocins. The structural gene encodes the pre-probacteriocin, the immunity gene encodes small proteins, genes encoding proteins for processing, transport and secretion of the pre-probacteriocin, genes encoding the enzymes for post-translational modifications and genes encoding components involved in the regulation of the synthesis.

regulated in function of certain environmental factors (Skaugen et al., 2003). The regulation process undergo by a signal transduction systems of three components that includes the inductor peptide (IP), an sensor histidine protein kinase (HPK) and response regulatory protein (RR). The complete process for bacteriocin production and secretion is shows in Figure 1. Two models have been proposed to explain the induction process, the inducing peptide and signal transduction mechanism.

The inducer peptides (IPs) are small cationic molecules that form an amphiphilic α helix and are the signal of the regulatory systems or "quorum sensing" that control the biosynthesis of certain bacteriocins. According to the model, the IP is produced constitutively in small amounts, thereby is accumulated progressively during cell growth, and when the levels required to exert the induction there is an increase in the expression of genes of the bacteriocin gene cluster.

The second model to explain the induction proposes that IP occurs at a level below that required for the self-induction, and in diverse environmental factors temporarily increases its production, so when required levels are exceeded, again, it induces its own synthesis and the remaining genes from the bacteriocin gene cluster (Figure 2) (Straume et al., 2007).

TRANSPORT SYSTEMS

Most proteins are synthesized as inactive precursors or pre-proteins with a signal sequence essential for the cell to recognize and transport an extracellular protein to the outside by two systems, the ABC-Transporter System or Dedicated Transportation System (DTS) and the General Secretory Pathway (GSP) or Sec System.

ABC-transport system or dedicated transportation system

ATP-binding cassette (ABC) proteins make up one of the largest superfamilies of proteins and are found in all living organisms. Most are membrane transporters that couple ATP hydrolysis to import or export of a large variety of substrates (Orelle et al., 2008).

A classic ABC-transporter includes four domains, two transmembrane domains (TMD) and two ATP-binding domains. Transmembrane domains are N-terminal, hydrophobic, and are integrated into the membrane, while the ATP-binding domains are C-terminal, hydrophilic, and are associated with the cytoplasmic face of the cell membrane. Typically, peptides function as four

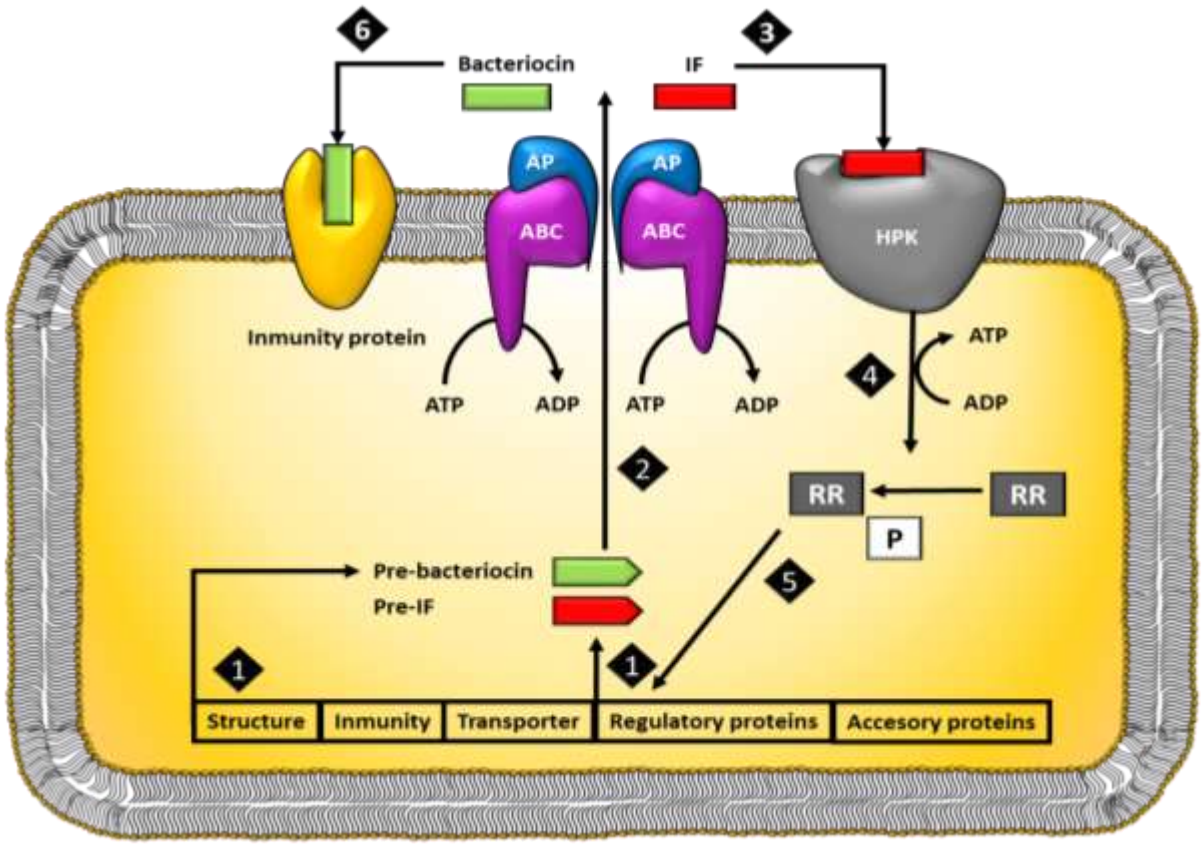

Figure 2. Biosynthesis of class II bacteriocins (modified of Chen and Hoover, 2003).

independent domains; however, in some cases, may act as a polypeptide complex (Locher, 2009).

The ABC-transporter system is also known as dedicated transport system (DTS), usually specific for a protein or group of proteins of the same family. The carrier protein (ABC) (1), the hydrophilic C-terminal with binding sites for ATP (2) and the accessory protein (PA) interacting with ABC type transporter are shown in Figure 3 (Kodali et al., 2013).

General secretory pathway (Sec)

Protein complexes of the Sec family are found universally in prokaryotes and eukaryotes. The peptides and proteins synthesized with an N-terminal signal peptide type (SP) are processed and secreted by the general secretory pathway (GSP). Secretion of peptides requires the participation of several components, the majority of the characteristics reference the translocase of *E. coli*. However, homologous systems have been described in *Bacillus subtilis* (Kuipers et al., 2006). The translocase in *E. coli* consists of three integral inner membrane proteins, SecYEG, and the cytoplasmic ATPase, SecA. SecA recruits SecYEG complexes to form the active translocation channel, and proteins are translocated through the SecY channel. A long α-helix in SecA is important for coupling of ATPase activity to protein translocation (Sanganna Gari et al., 2013).

PROMISING ACTION OF BACTERIOCINS TO BE CONSIDERED AS BIOTHERAPEUTICS

Bacteriocins are distinguished from antibiotics by two main characteristics: bacteriocins are ribosomally synthesized and have a relatively narrow killing spectrum (Riley and Wertz, 2002), and may be valuable biotherapeutic tools.

The biotherapeutic are medicines derived from proteins and/or different molecules produced by eukaryotic cells, bacteria and viruses, which have been applied in comprehensive and innovative treatments worldwide (Dobson et al., 2012). Some treatments use class I (nisin) and unmodified class IIa bacteriocins like pediocin, enterocin and divergicin for biotherapeutic application.

Pediocin PA-1 confirm its effect against *Listeria monocytogenes*, pathogenic bacterium that causes listeriosis, a serious infection spread by eating contaminated foods. The provision of purified pediocin

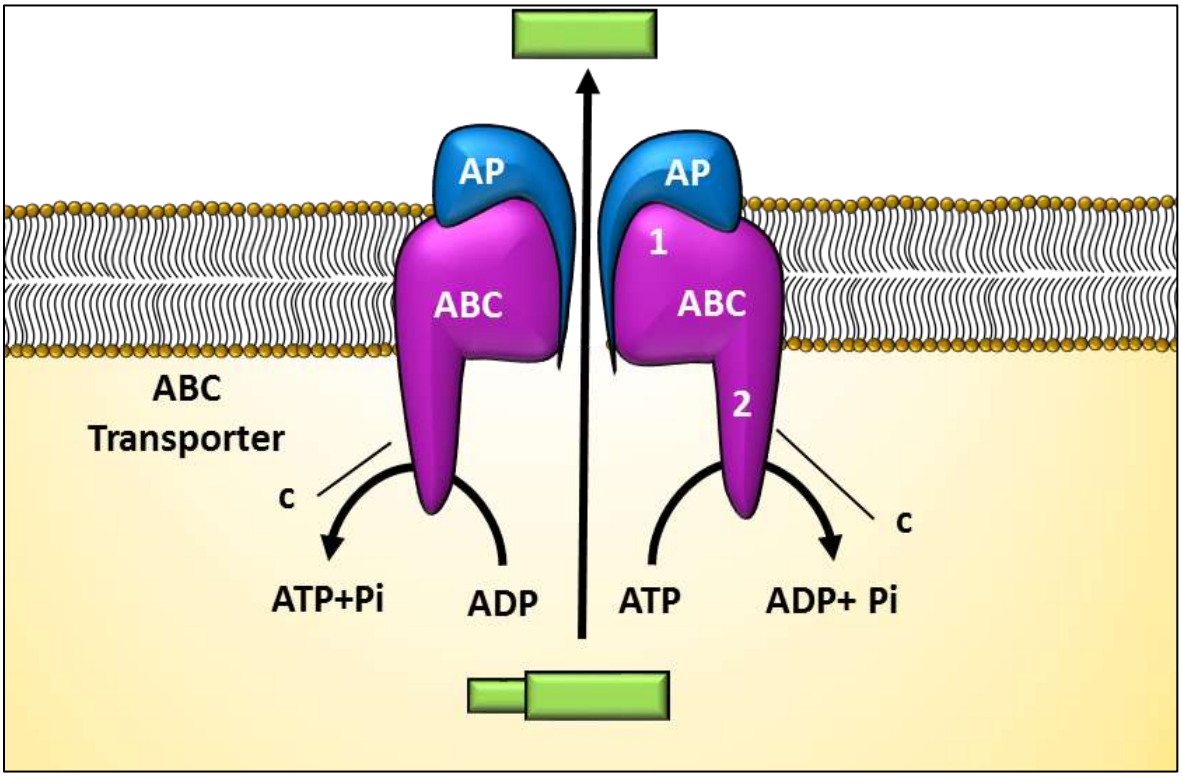

Figure 3. ABC-Transport System in Gram-positive bacteria (Adapted from Kodali et al., 2013).

intraperitoneally in mice as model systems infected with *L. monocytogenes*, reduces 100 times the total count of intestinal *Listeria*. This research confirms the effectiveness of treatment for the prevention of listeriosis by the action of the bacteriocin (Dabour et al., 2009). The enterocin E50-52 synthesized by *Enterococcus faecium* (NRRL B-30746) has been proven effective *in vitro* against *Staphylococcus aureus* resistant to methicillin (MRSA), showing capability for application as an alternative treatment without generating resistance antibiotics (Dobson et al., 2012).

The same bacteriocin in minimum inhibitory concentration (MIC) from 0.025 to 32 mg/mL was tested against *Campylobacter jejuni, Yersinia* spp., *Salmonella* spp., *E. coli* O157: H7, *Shigella dysenteriae, Morganella morganii, Staphylococcus* spp. and *Listeria* spp, showing significant results, for example, orally administered reduce up to 100, 000 fold for *C. jejuni* and *Salmonella enteritidis* in the intestine, and also minimizes the survival of *S. enteritidis* in the liver (Svetoch et al., 2008a, b).

Use of enterocin S760 for prophylaxis in dose 50 mg/kg during 10 days prevented lethal infection in 100% of mice, whereas its use for treatment cured 70% of animals with salmonellosis (Svetoch et al., 2010).

L. monocytogenes is a bacterial pathogen responsible for listeriosis, a foodborne disease characterized by septicemia and abortion in pregnant women, and it is also responsible for gastroenteritis in healthy individuals and for a severe invasive disease in immunocompromised patients. *In vivo,* the activity of divergicin V41 against *L. monocytogenes* EGDe administered intravenously in mice confirms its antilisterial activity and growth experiments revealed the reduce bacterial growth (Rihakova et al., 2010). The *L. monocytogenes* EGD-e contains a luciferase-based vector, pPL2lux, and use of this vector to study gene expression in *L. monocytogenes*. pPL2lux is a derivative of the listerial integration vector pPL2 and harbors a synthetic luxABCDE operon encoding a fatty acid reductase complex (LuxCDE) involved in synthesis of the fatty aldehyde substrate for the bioluminescence reaction catalyzed by the LuxAB luciferase.

Nisin F is a new lantibiotic bacteriocin produced by a *L. lactis* subsp. *lactis* Isolate from freshwater catfish (*Clarias gariepinus*), active against *S. aureus, Staphylococcus carnosus, L. curvatus, L. plantarum* and *L. reuteri.* The effectiveness of nisin F has been experimentally tested *in vivo* in rats that were infected with *S. aureus* (De Kwaadsteniet et al., 2008). Rats treated with nisin F administered intranasally (80-320 AU/mL) remained healthy. This preliminary evidence in animals should be confirmed in humans to control respiratory tract infections caused by *S. aureus* (De Kwaadsteniet et al., 2009).

The ability of nisin F to control *S. aureus* infection in the peritoneal cavity was studied in mice, and the suppresion

of growth of *S. aureus* was confirmed in the peritoneal cavity for at least 15 min (Brand et al., 2010). The use of bacteriocins such as biotherapeutics has been demonstrated not only in bacteriocins synthesized by lactic acid bacteria, besides there are reports of successful therapy with *Bacillus* bacteriocins. *Bacillus thuringiensis* is one of the most profitable entomopathogenic bacteria that has been used as a biopesticide due to its ability to synthesize insecticidal crystal proteins during sporulation and vegetative insecticidal proteins during the vegetative phase of growth. Also, it is important in this review because it may expand its potential by producing bacteriocins, thuricins named according to the subspecies that can synthesize these antimicrobial proteins (Chaabouni et al., 2012; De la Fuente-Salcido et al., 2013; Huang et al., 2014).

The most successful example is reported for thuricin CD, the bacteriocin synthesized by *B. thuringiensis* strain DPC 6431 whose activity has been proven effective as a biotherapy in the treatment of diarrhea associated with *Clostridium difficile* without collateral impact on the intestinal flora of patients treated (Rea et al., 2010, 2011). Another important field for biomedical application of bacteriocins from *B. thuringiensis* (morricin, kurstacin, kenyacin, entomocin and tolworthcin) is animal health. These bacteriocins were included in the study to determine their antagonism against pathogenic strains of *S. aureus* isolated of milk from diseased cows mastitis, confirming an high antibacterial activity (Barboza-Corona et al., 2009). Also these bacteriocins are effective against pathogens isolated from bovine clinical and subclinical mastitis, because it inhibit the growth of multiantibiotic resistance bacteria such as *Staphylococcus agnetis, Staphylococcus equorum, Streptococcus uberis, Brevibacterium stationis* and *Brachybacterium conglomeratum* (León-Galván et al., 2015).

The last examples strengthens the feasibility of the application of bacteriocins with high capacity to generate new models for future alternative treatments to antibiotics for preventing and/or reducing incidence of diseases in both human and animal infections.

Conclusion

The rise in antibiotic-resistant pathogens has increased efforts to develop new antibiotics active against the resistant bacteria. The diversity of bacteriocins is a trait that gives them numerous possibilities for application in medicine, therefore, knowledge on its structure, the steps involved in biosynthesis and transport, can lead to better understanding of the mode of action and improvement of their activity. It can also lead to the generation of new broad antimicrobial spectra peptides and increase the application of bacteriocin in human health and veterinary medicine with promising commercial potential.

Undoubtedly, the antimicrobial peptides such as bacteriocins have enough features to be recognized as the next generation of biotherapeutics to treat infections caused by multidrug resistant bacteria to traditional antibiotics.

Conflict of interest

The authors did not declare any conflict of interest.

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