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Review Article

Bacteriocin in Harmony with ABC Transporter Exhibits Antimicrobial Activity

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Abstract

Bacteriocins are antimicrobial peptides or proteins which are synthesized ribosomally by diverse bacteria and some archaea and exert antimicrobial activity via membrane permeabilization. They have been utilized as food preservatives for more than half a century and they have distinguished features for further applications as the next generation preservatives. In fermented foods, Lactic Acid Bacteria (LAB) displays a number of antimicrobial activities. Their ability to serve as a biopreservative is due to the production of various antimicrobial substances which include bacteriocin. The kinetics of bacteriocin production by LAB as a function of process factors have been studied in detail and the studies indicate that the bacteriocinogenic LAB strains may play a significant role in the food industry and several bacteriocins with industrial potential have been purified and characterized. *Lactococcus* sp. is generally regarded as safe bacteria and their bacteriocins are expected to be used for various applications. A number of lactococcal antimicrobial peptides, bacteriocins, have been discovered and characterized so far. On the basis of the safety of LAB, their bacteriocins are expected to be antimicrobial agents as well as food preservatives. Several genes like those encoding ABC transporters and other immunity proteins are involved in the biosynthesis of bacteriocins. Bacteriocins are translated as prepeptides with leader peptides and secreted by dedicated ABC transporters simultaneously with cleavage of N-terminal leader peptides. Peptide bacteriocins are exported across the cytoplasmic membrane by a dedicated ATP-binding cassette (ABC) transporter. This represents a novel strategy for secretion of bacterial proteins.

Keywords: *Lactic Acid Bacteria; Bacteriocin; Nisin; Leader Peptide; ABC Transporter*

Abbreviations

LAB: Lactic Acid Bacteria; ABC: ATP-Binding Cassette, HK: Histidine Kinase, RR: Response Regulators

Introduction

Lactic Acid Bacteria

Lactic Acid bacteria (LAB) are a group of Gram-positive, nonmotile, nonsporulating, microaerophilic or aerotolerant, rod and coccus-shaped bacteria, with low proportions of G+C in their DNA (< 55%); they produce lactic acid using either homofermentative or heterofermentative pathway. Generally, they lack catalase, although pseudo-catalase activity was detected in cultures grown on low sugar concentrations.

The Lactic acid bacteria include *Lactococcus, Lactobacillus, Leuconostoc, Streptococcus, Enterococcus, Aerococcus, Pediococcus, Tetragenococcus, Oenococcus, Vagococcus, Carnobacterium, Weisella* etc. Lactic acid bacteria are commonly found in foods products e.g. vegetables, fruits, beverages, fermented meat, and dairy products; in different parts of our body like intestinal and genital tracts, the respiratory tract of humans and animals; in sewage, and in plant materials. They are the most widely used bacteria as starter cultures for the industrial production of fermented dairy products, meat, vegetable and cereal products. This is because they have the unique ability

to break down carbohydrates, proteins and fats in food, help in the absorption process of essential minerals, amino acids and vitamins, produce aroma and flavour and retard food spoilage.

Although bacteriocins were previously categorized as antibiotics, they are not. The major difference between bacteriocins and antibiotics is that bacteriocins restrict their activity to strains of species related to the producing species and particularly to strains of the same species. Antibiotics on the other hand, have a wider activity spectrum and even if their activity is restricted this does not show any preferential effect on closely related strains. In addition, bacteriocins are ribosomally synthesized and produced during the primary phase of growth, though antibiotics are usually secondary metabolites [1]. Bacteriocins usually have low molecular weight (rarely over 10 kDa), they undergo posttranslational modification and can be easily degraded by proteolytic enzymes especially by the proteases of the mammalian gastrointestinal tract, which makes them safe for human consumption. Bacteriocins have differences with antibiotics in their application, synthesis, activity, tolerance, interaction, mode of action and toxicity [2].

Lactic acid bacteria may be successfully used chemical, pharmaceuticals, and other industries as a microorganism beneficial to humans, since they have several advantages in industrial fermentations:

a) they are easily digested by stomach acid and are non-pathogenic;
b) they are microaerophilic or aerotolerant with a very minimum oxygen demand
c) they grow rapidly, requiring a short fermentation process;
d) they are non- toxic
e) their growth discourages spoilage and contamination with other microorganisms;
f) they can secrete proteins;
g) they can ferment a wide range of cheap substrates such as milk, whey, plant wastes, and hydrolyzed starch;
h) they have been used in the food industry for years.

Consequently, methods for their cultivation on a large scale already exist.

The preservative effect of lactic acid bacteria during the production and subsequent storage of fermented foods is mainly due to the acidic environment that prevails. This lowering of pH is attributed to the fermentative conversion of lactose to organic acids and is an important characteristic that leads to an increased shelf-life and safety of the fermented end product. In recent years, it has become clear that the overall inhibitory action of lactic acid bacteria is due to their ability to produce and excrete inhibitory substances other than lactic acid and acetic acid. These substances are active against a broad spectrum of microorganisms, and thus can make significant contributions to their preservative action.

Source of bacteriocin

A great number of strains of lactic acid bacteria (LAB) have been found to produce bacteriocins. It seems that bacteriocins play important roles in bacterial competition and that bacteriocin-producing bacteria have considerable advantages to survive their environments. Lactic acid bacteria (LAB) have a long history of application in fermented foods because of their beneficial influence on nutritional, organoleptic, and shelf-life characteristics [3]. They cause rapid acidification of the raw material through the production of organic acids, mainly lactic acid. In addition, production of acetic acid, ethanol, aroma compounds, bacteriocins, exopolysaccharides, and several enzymes is of importance. Whereas a food fermentation process with LAB is traditionally based on spontaneous fermentation or backslopping, industrial food fermentation is nowadays performed by the deliberate addition of LAB as starter cultures to the food matrix.

LAB is generally known to be a part of human commensal resident microflora. Long history of its human consumption as well as human exposures led to the conclusion that they are generally safe. On the basis of the safety of LAB, their bacteriocins are expected to be antimicrobial agents as well as food preservative [2]. Whereas general clinical antibiotics are synthesized as secondary metabolites generally by microorganisms not related to foods, LAB bacteriocins are synthesized ribosomally as primary metabolites in accordance with cell

growth by food-borne bacteria. In addition, although antibiotics are generally needed at micromolar level for their activity, bacteriocins act specifically to target bacteria only at nanomolar level. No side effects and no developments of resistant bacteria have been reported in practical usage of bacteriocins. One of the reasons is that bacteriocins act through quick pore formation on the target cell membrane at extremely low concentrations. Moreover, since bacteriocins have proteinaceous nature, they can be degraded easily in our bodies and other environments. It means that bacteriocins do not remain in the environment and give few chances to bacterial strains in the environments to develop resistance, although pollution of environments by residues of antibiotics is an emerging problem. The most well-studied bacteriocin, nisin A, produced by strains belonging to *Lactococcus lactis* has been used as a food preservative in more than 50 countries without the emergence of resistant bacteria. But in laboratory experiments, Nisin resistance can be grown by successive exposure to Nisin.

LAB bacteriocins are normally small (< 10 kDa) cationic, heat-stable, amphiphilic and membrane permeabilizing peptides. They are divided in three major classes. Their classification was constantly revised throughout the last decade with extensive research [4,5] and are still going on.

These bacteriocins appear to exhibit relatively little adsorption specificity. Cell wall of Gram positive (+) bacteria permits passage of relatively large molecules. Cell surface polymers mainly anionic which are part of the cellular wall like teichoic and lipoteichoic acids, are important in the initial interaction of anionic bacteriocins produced by Gram positive (+) bacteria. LAB bacteriocins have greater antibacterial activity at lower pH values (below 5) because their adsorption to the cell surface of Gram positive (+) bacteria is pH dependent. There are amino acid sequence homologies in the mature peptide within the N-terminal leader region and in the associated proteins in secretion and processing [6]. In 1928 nisin A produced by *L. lactis* was discovered from a fermented milk [7] and various LAB bacteriocin including lactococcal ones have been discovered [8]. Different methods of classification criteria have been used to classify the bacteriocins produced by gram-positive bacteria.

Bacteriocins are agents which are responsible for killing or inhibiting the closely related species or even different strains of the same species. Bacteriocins are encoded by bacterial plasmids. Bacteriocins are named after the species and hence in literature one encounters various names e.g., leucocin from *Leuconostoc gelidum*; pedicocin from *Pediococcus acidilactici*; sakacin from *Lactobacillus sake* etc. Bacteriocins can be classified into four groups on the basis of their molecular mass, thermostability, enzymatic sensitivity, presence of posttranslationally modified amino acids, and mode of action according to Klaenhammer T R [9] and Cotter PD., *et al*. [8]. Bacteriocins of Gram positive bacteria including LAB bacteriocins have been divided into four classes according to their structures and characteristics [9]. A new bacteriocin from *Lactococcus lactis* JC10, isolated from perishable papaya fruit, has shown a wide range of temperature and pH stability, very less production time and broad spectrum of antimicrobial activity [10].

Biosynthesis of bacteriocin

Several genes like those encoding ABC transporters bacteriocin prepeptides and other immunity proteins are involved in the biosynthesis of bacteriocins. Class I bacteriocins require genes encoding modification enzymes [11].

Nisin A prepeptides as class I bacteriocin are matured by modification enzymes and secreted. Bacteriocins are translated as prepeptides with leader peptides, and secreted by dedicated ABC transporters simultaneously with cleavage of leader peptides. Bacteriocins without leader sequences are also found e.g. LacticinQ [12] and that some other bacteriocins such as lactococcin 972 are secreted via secondary pathway and have no dedicated transporter [13].

Some bacteriocins such as nisin A production is controlled by the quorum sensing mechanism, a mechanism by which bacteria regulate gene expression in accordance with population density. This widespread bacterial mechanism employs additional genes for the two (three) component regulatory system [14,15].

This system is used for class IIa bacteriocin production. The biosynthesis of two-peptide bacteriocins is transcriptionally regulated through a three-component regulatory system. The components are i) a membrane-interacting peptide pheromone, ii) a membrane-associated histidine protein kinase (HK) and iii) response regulators (RR).

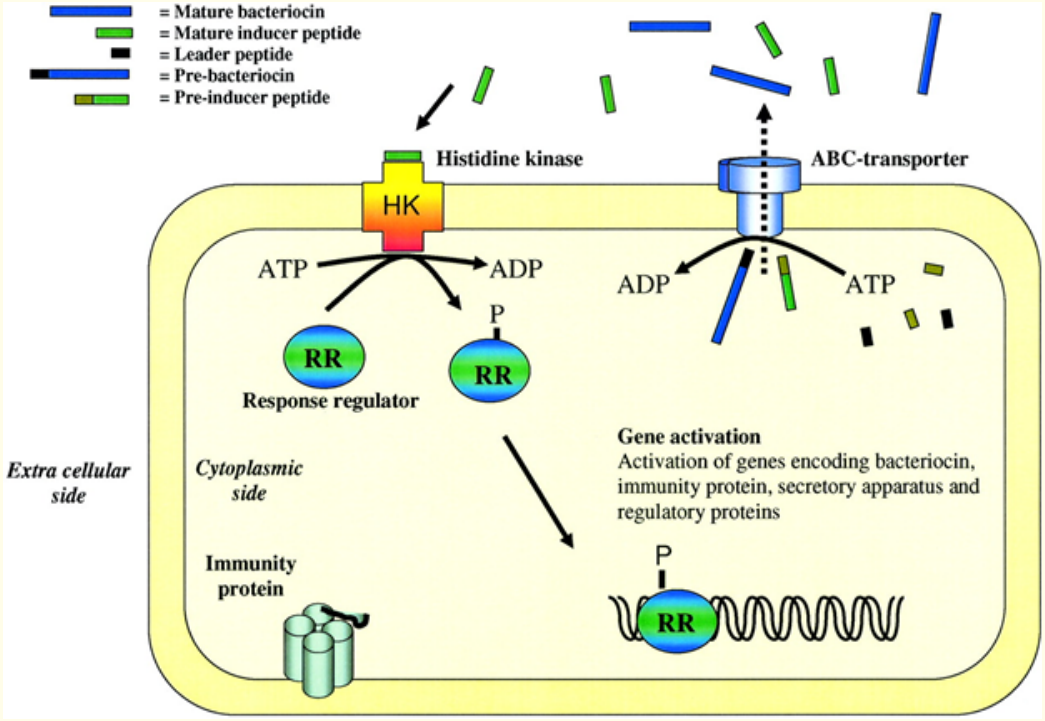

Figure 1: *Schematic presentation of the biosynthesis of a class IIa bacteriocin [16].*

Ribosomally synthesized matured prebacteriocin and preinducer peptides are secreted through the ABC transporter. Mature inducer peptide interacts with Histidine Kinase (HK) receptor which is autophosphorylated at the cytoplasmic side. Response Regulators (RR) get activated after getting attached to phosphate groups. RR acts as a transcriptional activator in this process.

ABC transporter

ABC is a superfamily where it produces one of the largest protein family with a diverse of physiological functions. ABC super families of transporters are expressed in microorganisms, plants and mammals and are involved in the transport of chemically diverse compounds across membranes. ABC transporters catalyze transport reactions, such as the high-affinity uptake of micronutrients into bacteria and the export of cytotoxic compounds from mammalian cells. Crystal structures of ABC domains and full transporters have provided a framework for formulating reaction mechanisms of ATP-driven substrate transport, but recent studies have suggested remarkable mechanistic diversity within this protein family. ABC transporters take up a large variety of nutrients, biosynthetic precursors, trace metals and vitamins, while exporters transport lipids, sterols, drugs, and a large variety of primary and secondary metabolites. ABC proteins also transport a number of substrates including peptides, amino acids, sugars and a large number of hydrophobic compounds and metabolites across the plasma membrane and also intracellular membranes.

The conventional ABC transporter families consist of the ABCA, ABCB, ABCC, ABCD, ABCE, ABCF and ABCG families. In ABC transporter 11 clusters are present based on Ward clusture which mainly consisted of (1) prokaryotic macrolide-specific transporters, (2) ABC-2 prokaryotes, (3) ABCDs, fused PK-type ABC transporters, *yojI*, and miscs, (4) ABCGs, (5) ABCG (N-NBD) eukaryotes, (6) ABCA eukaryotes, (7) ABCB eukaryotes, (8) ABCB eukaryotes and similar prokaryotes, (9) ABCC (C-NBD) eukaryotes, (10) ABCC (N-NBD) eukaryotes, and (11) ABCC eukaryotes and similar prokaryotes.

ABCC (MRP) is a subfamily among the ABC transporters shown to have important functions across evolution. Mutations in ABCC1 (MRP1) cause drug resistance and immune response in humans. In plants, *Arabidopsis thaliana* ABCC1 is present in vacuolar membranes and is known to transport glutathione (GSH) conjugate and folates [17,18]. Studies with AtMRP1 showed MgATP-energized, vanadate-inhibitable, uncoupler-insensitive uptake of several glutathione (GSH) conjugates (GS-conjugates) which include N-ethylmaleimide-GS (NEM-GS), S-(2,4-dinitrophenyl)-GS (DNP-GS), glutathionylated chloroacetamide herbicides, (metolachlor-GS), folates and antifolates e.g. methotrexate (MTX) mediated by this protein in isolated vacuoles [19] or in vacuolar membrane vesicles purified from plants [17,18,20]. Also, AtMRP1 nucleotide binding domain contributes to arsenic stress tolerance with serine triad phosphorylation [21].

Relation of bacteriocin with ABC transporter

Peptide bacteriocins are exported across the cytoplasmic membrane by a dedicated ATP-Binding Cassette (ABC) transporter. Several studies have shown that there is a correlation between the functional characterisation and the phylogenetic classification of the ABC transporter. Based on phylogenetic and functional classification more than fifty subfamilies have been described which includes ABC-type bacteriocin transporter. Both importing and exporting ABC transporters are found in bacteria. The conserved ATP binding motif can be found in all bacterial export subfamily. Removal of the leader peptide from its substrate and its translocation of the substrate across the cytoplasmic membrane effectively prevent the mature and active bacteriocin from remaining in the cytoplasm. So bacteriocin ABC transporter has a dual function. Firstly, removal of the leader peptide from its substrate, and secondly translocation of bacteriocin across the cytoplasmic membrane. This represents a novel strategy for secretion of bacterial proteins. So, the interaction and transport of bacteriocin with ABC transporter is very important. Bacteriocin ABC transporter contain three domains on the same polypeptide consisting of a N-terminal proteotolytic domain, a hydrophobic internal membrane domain and a cytoplasmic C-terminal ATP binding domain. Two polypeptide appear to be required for the bacteriocin ABC transporter to be functional. The N-terminal peptidase domain that belong to MEROPS peptidase family C39 (clan CA), a central multi-pass transmembrane region and a C-terminal ABC transporter domain. These transporters have dual function. They remove the N-terminal leader peptide from its bacteriocin precursor by cleavage at a Gly-Gly bond and they transport the mature bacteriocin across the cytoplasmic membrane. The gene encoding the bacterial ABC transporter is actually part of the bacteriocin operon or can be found near the bacteriocin operon [22]. This represents a novel strategy for secretion of bacterial proteins. Many bacteria are known to regulate diverse physiological processes through this system which include bioluminescence, regulation of sporulation, virulence factor expression, antibiotics production, competence for genetic transformation, and activation of biofilm formation.

Lantibiotic and non-lantibiotic bacteriocins are synthesized as precursor peptides containing N-terminal leader peptides which are cleaved off during maturation. Most non-lantibiotics and also some lantibiotics have leader peptides of the so-called double-glycine type. These leader peptides share consensus sequences and also a common processing site with two conserved glycine residues in positions -1 and -2. The double-glycine-type leader peptides are unrelated to the N-terminal signal sequences which direct proteins across the cytoplasmic membrane by the secretory pathway. Their processing sites are also different from typical signal peptidase cleavage sites which suggest that a different processing enzyme is involved. A bacteriocin system gene pair with a fairly wide distribution in bacteria consists of a lactococcin 972 homologue and a multiple-membrane-spanning putative immunity protein. This entry represents a small clade within the ABC transporters that are encoded adjacent to these bacteriocin system gene pairs and are likely to function as export proteins.

Relationship of bacteriocin with ABC transporter is very close and found in many bacteria. In response to bacteriocin nisin A expression, a ABC transporter, srtFEG which is located downstream of srtRK was increased. However, srtEFG expression was not induced by nisin A in the srtRK mutant. Since *srtF* was homologous to *nisF*, which has been reported to be one of the ABC transporter clusters of *nisFEG*, plays a role in self-immunity against nisin A-producing *L. lactis* [23]. In *Staphylococcus aureus*, activation of BraSR leads to the upregulation of transporter *DE* expression that encodes an ABC transporter playing a key role in bacitracin and nisin resistance. Another ABC transporter is VraDE but its exact mechanism is unknown; however, the resistance is most likely based on an ATP-driven efflux mechanism [24]. The role of cellular response to membrane stability in the ABC transporter self-resistance mechanism in presence of bacterio-

cin is also important. The possible role of cellular response to membrane stability alterations and of multi-drug resistance ABC transporters as additional self-resistance mechanisms toward the lantibiotic was confirmed by proteomic and confocal microscopy experiments on a Microbispora ATCC-PTA-5024 lantibiotic-null producer strain which was exposed to an externally-added amount of NAI-107 during growth [25]. To gain immunity against nisin, the producing strain is expressing an ABC transporter called NisFEG, which expels nisin from the membrane. As a result, six to eightfold more nisin is needed to affect the cells. The hydrolysis of ATP by NisFEG is required for this immunity as shown by a mutant, where the ATP hydrolysis was disrupted. Also NisFEG recognizes the C-terminus of nisin and the deletion of the last six amino acids and the last ring lowered the fold of immunity displayed by NisFEG [26]. In *Lactobacillus plantarum* LR/14 in Escherichia coli BL21 (DE3) strain the heterologous expression, purification, and characterization of PlnE pre-peptide, ABC transporter (PlnG), and accessory protein (PlnH) were also reported [27]. In lactococcin Q the gene cluster was sequenced and in the downstream of the lactococcin Q structural genes (laqA and laqB) genes encoding lactococcin Q immunity (laqC), an ATP-binding cassette transporter (laqD) and a transport accessory protein (laqE) was found [28].

Discussion

Recent progress with the X-ray crystal structure determination of a variety of bacterial ABC transporters has helped to advance our understanding of the ATP hydrolysis-driven transport mechanism but has also illustrated the large structural and functional diversity within the family. Food-grade lactic acid bacteria produce many bacteriocins. It is proposed that bacteriocin mediated transmembrane ion flow result in cytotoxic effects, drop in intracellular pH and inhibiting enzymatic processes. Scientists use this phenomenon to direct or prevent the development of specific bacteria in food which becomes useful in maintaining rules in food safety. Development of desirable flora in fermented food can also be maintained by this. Results demonstrate that the ABC transporter has a dual function with removal of the leader peptide from its substrate and translocation of its substrate across the cytoplasmic membrane. This represents a novel strategy for secretion of bacterial proteins. Bacteriocins are synthesized as precursor peptides containing N-terminal leader peptides which are cleaved off during maturation. ABC transporter removes the N-terminal leader peptide from its bacteriocin precursor by cleavage at a Glycine-Glycine bond and they transport the mature bacteriocin across the cytoplasmic membrane. This represents a novel strategy for secretion of bacterial proteins. Although the role of ABC transporter on the antimicrobial activity of bacteriocin has been known, further research needs to be carried out where modifying ABC transporter might lead to enhanced efficiency of bacteriocins. In the past two decades, vast numbers of bacteriocins were being discovered but the only commercially available and industrially utilized bacteriocin is Nisin. Many novel bacteriocins with unique properties have been reported and it is clear that that there is still more to learn about this family of peptide antibiotics. So, in order to fight against some undesirable microorganisms further enhancement in the bacteriocin research against spoilage and pathogens are important. The mode of antimicrobial action and biosynthetic mechanisms of known bacteriocins are needed and the search for more novel bacteriocins with promising properties must continue [29-31].

Conclusion

An ABC transporter expels bacteriocin from cytoplasm through membrane. The N terminal leader peptide takes the bacteriocin to the cell membrane and the double Glycine type bond cleavage in leader peptide becomes important for the expulsion. Leader peptides share consensus sequences and also a common processing site with two conserved glycine residues in positions -1 and -2 which are unrelated to the N-terminal signal sequences in directing proteins across the cytoplasmic membrane by the secretory pathway. Peptide processing sites are also different from typical signal peptidase cleavage sites which suggest that a different processing enzyme is involved in this pathway.

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Volume 8 Issue 1 May 2017