

# Biosynthesis and Genetics of Lactic Acid Bacteria Bacteriocins

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Lactic acid bacteria (LAB) constitute a ubiquitous bacterial group that is widespread in niches of fermented food and gastrointestinal tracts of humans and many animals. LAB are especially known for their ability to produce lactic acid as the main end-product. These microorganisms also possess the ability to synthesize a wide variety of bioactive metabolites, belonging to different classes of chemicals including diacetyl, hydrogen peroxide, antibiotics, and bacteriocins.

Keywords: bacteriocins ; lactic acid bacteria ; biosynthesis

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## 1. Classification of LAB Bacteriocins

There are several classification schemes based on the biochemical and structural features of LAB bacteriocins. In 1993, Klaenhammer et al. suggested a classification system that divides LAB bacteriocins into four groups <sup>[1]</sup>. The class I bacteriocins are lantibiotics, which are small membrane-active peptides (<5 kDa) containing uncommon amino acids such as lanthionine,  $\beta$ -methyl lanthionine, and dehydrated residues. Class II includes small heat-stable peptides without lanthionine residues. Class III comprises large heat-labile proteins, while class IV is composed of large peptides complexed with carbohydrates or lipids. Cotter et al. (2005) performed a thorough modification of Klaenhammer's classification scheme and they grouped bacteriocins into just two categories: lantibiotics (class I) and non-lanthionine-containing bacteriocins (class II). They also suggested that the high-molecular weight thermolabile peptides (previously class III) should be designated as "bacteriolysins", and the previous class IV should be extinguished <sup>[2]</sup>. Cotter's classification scheme was broadly accepted for a long time, and has continuously been modified by researchers, since the repertoire of bacteriocins is rapidly growing <sup>[3][4][5]</sup>.

In general, class I bacteriocins are produced as precursor peptides that undergo extensive post-translational modifications. The mature peptides contain unusual amino acids, such as 2,3-didehydroalanine, D-alanine, and 2,3-didehydrobutyrine, as well as characteristic lanthionine rings that result from thioether formation between the side chains of cysteine and serine or threonine. Class Ia bacteriocins, which include nisin, consist of cationic and hydrophobic peptides that form pores in target membranes and have a flexible structure compared to the more rigid class Ib. Class Ib bacteriocins, which are globular peptides, have no net charge or a net negative charge. Class Ic is a growing class of two-component lantibiotic systems that utilize two peptides that are each posttranslationally modified to an active form and act in synergy to provide antibacterial activity. More detailed information on the structure and biosynthesis of lantibiotics is presented in previous ones <sup>[6][7][8]</sup>.

Class II bacteriocins are a class of small non-lanthionine-containing peptides. Unlike the lantibiotics described above, class II bacteriocins are less modified; a disulfide bridge and some N-terminal modifications are known to exist in some class II bacteriocins. Class II bacteriocins are divided into four subclasses, IIa, IIb, IIc, and IId. Subclass IIa bacteriocins are the most thoroughly studied. They are also known as pediocin-like peptides with antilisterial activity <sup>[9]</sup>. The class IIb bacteriocins (two-peptide bacteriocins) require two different peptides for optimal activity <sup>[10]</sup>. Class IIc bacteriocins are referred to as circular bacteriocins whose ring structure is formed in a head-to-end fashion <sup>[11]</sup>. Class IId bacteriocins are categorized as bacteriocins that have no significant sequence similarity to the other class II bacteriocins <sup>[12]</sup>.

## 2. Biosynthesis and Genetics

### 2.1. IIa

Class IIa bacteriocin is first ribosomally synthesized as a prebacteriocin, which contains an N-terminal leader sequence to keep the peptide inactive. The leaders contain 15 to 30 residues, most of which are featured for the double-glycine residues upstream of the cleavage site. The leader is believed to serve as a signal sequence for the processing and

secretion of bacteriocins by a dedicated system comprising an ABC transporter and an accessory protein. ABC-transporter protein contains the C-terminal ATP-binding domain and the N-terminal transmembrane domain embedded in the membrane bilayer. The N-terminal region can cleave the leader peptide at the double-glycine motif. The binding of prebacteriocin with N-terminal proteolytic domain triggers the ATP hydrolysis and subsequent conformational changes of the transporter, resulting in leader cleavage and translocation of the mature bacteriocin across the membrane [9]. The accessory proteins are postulated to facilitate the membrane translocation and/or help in the processing of the leader peptide [9]. For some class IIa bacteriocins, the accessory protein ensures the formation of correct disulfide bond formation [13]. However, not all class IIa bacteriocins are transported via ABC-transporter. Some bacteriocins including enterocin P, bacteriocin 31, enterocin SE-K4 lack the double-glycine motif in their leaders and are exported by sec-dependent translocation system [14][15][16]. These bacteriocins have a hydrophobic N-terminal sec-dependent leader to direct the secretion of the prebacteriocins. The leader was removed by a signal peptidase during translocation.

The synthesis of class IIa bacteriocins is typically regulated by a quorum sensing (QS) system that consists of three components, an inducing peptide, a membrane-associated histidine protein kinase (HPK) and a cytoplasmic response regulator (RR). The inducing peptide is initially synthesized as a prepeptide with N-terminal leader sequence, which is cleaved upon secretion by the ABC-transporter. The concentration of inducer peptide increased along with cell growth. An excess in inducer peptide concentration activates the three-component system by triggering the autophosphorylation of HPK, which transfers a phosphate group to its cognate RR. The phosphorylated RR acts as a transcriptional activator and activates the expression of biosynthetic gene clusters. Moreover, environmental parameters may influence the production of class IIa bacteriocin by acting on the bacteriocin regulatory system or affecting the binding of the induction peptide to HPK [17].

The bacteriocin-producing bacteria avoid killing by their own bacteriocins through the co-expression of immunity proteins. Immunity proteins for the class IIa bacteriocins range from 81 to 115 amino acids in length and display substantial variation in their sequences. The C-terminal region is involved in specific recognition of their related bacteriocins. However, "cross-immunity" against other class IIa bacteriocins was observed [18]. The immunity protein folds into a globular protein in an aqueous solution and contains an antiparallel four-helix bundle [19]. There are currently two models being proposed regarding the mechanism of immunity protein: (i) the immunity protein directly interacts with the bacteriocin to obstruct pore formation; (ii) the immunity protein binds to the cytoplasmic side of the receptor and blocks the receptor's ability to interact with the bacteriocin. Although direct evidence of contact between the immunity protein and bacteriocin has not been obtained, there are experimental data to support the first model. The expression of MunC protein (enterocin CRL35 immunity protein) in *E. coli* is sufficient to prevent the lethal effects of the hybrid suicide probe EtpM-enterocin CRL35. *E. coli* is naturally insensitive to enterocin CRL35, since it does not express the receptor. These results prove that the immunity protein MunC can protect bacterial cells in the absence of the receptor [20]. The second model of "indirect immunity protein and bacteriocin binding" was recently proved experimentally. When the bacteriocin targets the membrane from the outside, it gets locked onto the receptor by its immunity protein by forming a ternary complex. For pediocin PA-1, both IIC and IID components of the man-PTS play an important role in the specific recognition between the bacteriocin-receptor complex and the immunity protein PedB [21].

Production of class IIa bacteriocins is often associated with the presence of a plasmid. In some situations, the biosynthetic gene clusters could be located in the chromosome, as exemplified by enterocin A, divercin V41, sakacin P and canobacteriocin B2 and so on. The genetic organization of this class shows considerable conservation. The gene cluster encoding class IIa bacteriocins usually also contain an operon that encodes ABC-transporters and their accessory proteins. The bacteriocin structural genes are generally located in a small operon with the immunity genes, with the exception of divercin V41, mundicin KS and mundicin L. For most class IIa bacteriocins, three genes encoding the regulatory system are located in the same operon, in which the two genes encoding HPK and RR follow the gene encoding the inducing peptide. Intriguingly, the sakacin G gene cluster contains duplicated structural genes skgA1 and skgA2 that encode essentially identical bacteriocin. The leader sequence of SkgA1 and SkgA2 differed only by three residues [22].

## 2.2. IIb

Similar to some class IIa bacteriocins, class IIb bacteriocins are initially synthesized as precursor peptides containing N-terminal extensions (leader peptides) which are cleaved off during maturation. All class IIb bacteriocins identified so far contain a double-glycine-type leader. The ATP-binding cassette (ABC) transporter and an accessory protein lead to the cleavage of inactive pre-peptide with the concomitant export of the mature bacteriocin across the cytoplasmic membrane. The accessory protein may be involved in immunity against the bacteriocin or required for secretion of the bacteriocin.

However, for some two-peptide bacteriocins such as sakacin T, the processing and secretion are solely dependent on the ABC-transporter since the gene encoding the accessory protein is absent [23].

The production of class IIb bacteriocins was commonly regulated by a three-component regulatory system. The inducing peptide acts as an indicator of the cell density, which is sensed by the corresponding HK, resulting in the activation of the RR, which then activates the expression of all operons necessary for bacteriocin synthesis, transport, and regulation. The best example of such a regulatory system is the production of plantaricin E/F and plantaricin J/K by *L. plantarum* C11. The inducing peptide plantaricin A is secreted at low basal levels, thus enabling the bacterium to sense its own growth. At a certain threshold level of plantaricin A, an autoinduction loop is triggered, which leads to massive production of plantaricin E/F and plantaricin J/K [24]. Notably, there are two RRs encoded by *L. plantarum* C11, PlnC and PlnD. It has been shown that PlnC activates while PlnD represses the genes involved in bacteriocin synthesis [25]. However, truncated versions of the activator PlnC, resulting from the translation from alternative start codons within plnC, were found to exhibit repression on the bacteriocin biosynthesis operon [26]. Moreover, *L. lactis* MG1363 produced supernatants acting as environmental signals which can switch on bacteriocin production in *L. plantarum* NC8 via a quorum-sensing mechanism mediated by the inducing peptide PLNC8IF [27].

The mechanism of how immunity proteins protect producing cells from class IIb bacteriocins was not fully elucidated. Some immunity proteins, including plnI for plantaricin EF and plnLR for plantaricin JK, show homology to the Abi family of proteins, which are putative membrane-bound metalloproteases characterized by three conserved motifs. These immunity proteins probably function by proteolytically degrading their cognate bacteriocins [28]. Other immunity proteins, including the immunity protein for lactococcin G, likely interact directly both with the bacteriocin and its cellular receptor [29]. So far, all the immunity proteins for class IIb bacteriocins are predicted to contain transmembrane domains (TMD). However, they range in length, number of TMDs, and orientation across the membrane. The smallest immunity protein, CbnZ for carnobacteriocin XY, has just 42 amino acids and contains as few as one TMD, while LagC is a membrane-associated protein with four TMDs [30]. The wide structural variety of immunity proteins may be attributed to the fact that class IIb bacteriocins adopt different receptors as targeting molecules.

A typical gene set for class IIb bacteriocin production comprises five to eight genes [31][32][33]. These include two bacteriocin encoding genes, whose closely adjacent gene encodes the immunity protein. The genes encoding a three-component regulatory system may locate up- or downstream of the bacteriocin structural genes. Most class IIb gene clusters also have two genes encoding an ABC transporter complex.

### 2.3. IIc

Three key steps are involved in the biosynthesis of circular bacteriocins: cleavage of the leader, circularization, and exportation of the mature bacteriocin. Leader cleavage is believed to be the first step in the maturation and a requirement for further processing into the mature bacteriocins. The leader peptides ranging between 2 and 35 amino acids share no sequence similarity and the function of the leaders awaits further investigation. Unlike class IIa and IIb bacteriocins, whose leader was generally cleaved at the double-glycine site, there is no common recognition site for leader cleavage of circular bacteriocins. Moreover, the enzymes responsible for the cleavage of the leader peptide have not yet been identified.

The exact mechanism of the circularization reaction for circular bacteriocins is not fully understood. The ligation sites of all circular bacteriocins are located within a helical structure, consisting mainly of stretches of hydrophobic residues. It was suggested that the hydrophobic environment is essential for the circularization reaction [11]. The properties of both the N- and C-terminal residues are critical to the efficiency of the circularization process. For AS-48, the substitution of Met1 to Ala lowered the circularization efficiency significantly, whereas the substitution of Trp70 (last residue) to Ala resulted in the production of both circular and linear forms of the bacteriocin [34]. Mutational analysis at the Leu1 position of enterocin NKR-5-3B revealed that only mutations with helix structure-promoting hydrophobic residues (Ala, Ile, Val or Phe) were able to yield the mature Ent53B derivative [35]. These results highlight the importance of the hydrophobic nature of ligation points for the circularization mechanism. Most of the proteins encoded by the biosynthetic gene clusters contain multiple putative membrane-spanning domains and are probably associated with the membrane. The circularization reaction may be catalyzed by a membrane-located protein complex [36]. Such a complex may be also responsible for exporting circular bacteriocins in a manner of coupling circularization and secretion reactions.

Several proteins have been identified to be involved in immunity to circular bacteriocins. As-48D1, Gaal, and CcII are the dedicated immunity proteins for AS-48, gassericin A, and carnocyclin A, respectively [37][38][39]. These immunity proteins are small (49–56 amino acids), cationic (high pI), and contain one or two transmembrane domains, suggesting that they

may be located in the cell membrane. These immunity proteins can provide a certain level of immunity to their cognate bacteriocins. Full immunity requires the combined activity of several other proteins.

Circular bacteriocin gene clusters often consist of overlapping genes, demonstrating a tight organizational structure or genes which depend upon the ribosomal binding site of upstream genes. This indicates that expression is regulated by translational coupling. The minimal set of genes required for bacteriocin production and immunity, in general, comprises 5 to 10 genes [40]. Interestingly, the bacteriocin structural genes are not adjacent to the immunity genes, some of them are located in different operons. The transportation system of class IIc bacteriocins is usually more complex than other class II bacteriocins. They have an accessory operon (ccIEFGH, as-48EFGH, garEFGH) encoding an ABC transporter complex, consisting of a permease, an ATPase, and an extracellular protein.

## 2.4. IId

Most of the leaderless bacteriocins remain to be studied in more detail regarding the biosynthetic mechanism. The leader sequences of other general bacteriocins play an important role in the recognition by transporters. Moreover, the leader sequences keep the precursor peptides inactive during biosynthesis inside the host until the appropriate time for secretion. How leaderless bacteriocins are recognized by transporter protein and secreted remains elusive. A distinguishing feature of leaderless bacteriocins is the presence of a formylated N-terminal methionine residue. Interestingly, lactocins Q expressed in *E. coli* BL21(DE3) has unformylated methionine at the N-terminal. Nevertheless, the peptide demonstrated antimicrobial activity against several of the indicator strains tested [41]. Thus, leaderless bacteriocins may not require a formylated N-terminus for full activity. However, more studies are needed to decipher the importance of the formylated methionine at the N-terminus for the biosynthesis of leaderless bacteriocins. The leaderless bacteriocins are active immediately after their translation process. The transport and immunity of leaderless bacteriocins may be carried out by one protein or protein complex. LmrB, an ABC-type multidrug resistance transporter, has been shown to be involved in both the secretion and self-immunity of this leaderless bacteriocin [42]. The secretion of lacticin Q is strictly controlled by the presence of LmqBCDEF complex, whereas immunity is flexible in that LmqEF (ABC transporter) is the minimal unit required for sufficient immunity and LmqBCD could be considered an accessory protein that supports the activity of LmqEF [43]. This may indicate that leaderless bacteriocins have in common the feature of having one dedicated ABC transporter mediating both secretion and immunity. However, recently it was showed that the ABC transporter is only involved in the transport but not the immunity of enterocin DD14, a leaderless two-peptide bacteriocin. The intracellular enterocin DD14 plays a role in its own immunity system [44].

Similar to class IIa and IIb bacteriocins, the non-pediocin liner bacteriocins are synthesized as biologically inactive pre-peptides consisting of an N-terminal leader peptide. Following synthesis of the pre-peptide, cleavage of the N-terminal leader sequence generally occurs at the double glycine site by means of a dedicated membrane protein from the ATP-binding cassette transporter family. In addition, a number of non-pediocin liner bacteriocins including lactococcin 972 and divergicinA are secreted through a general sec-dependent pathway and their leaders are cleaved by extracellular signal peptidase. Most LAB have a dedicated immunity protein to protect the cells from their own non-pediocin liner bacteriocins. It is not clear if there is a common mechanism of immunity for non-pediocin liner bacteriocins. For Lactococcin A, its immunity protein LciA has a similar four-helix bundle fold with the immunity proteins of the pediocin-like bacteriocins. Interestingly, LciA and the pediocin-like immunity proteins function in a similar manner. They bind to the bacteriocin–man-PTS complex and prevent membrane leakage [45].

The gene clusters for most of the leaderless bacteriocins have been identified. Genes involved in transport and immunity are often closely associated with bacteriocin structural genes. Leader-containing bacteriocins need an accessory protein function together with the cognate ABC transporter to mediate bacteriocin secretion. Such an accessory protein is not required for transporting leaderless bacteriocins. Moreover, genes related to formylase synthesis were not found in the vicinity of the bacteriocin structural gene, indicating that the N-terminal formylation of leaderless bacteriocins may be carried out by a host-encoded formylase that exists outside of the biosynthetic gene cluster [11][46]. Interestingly, the structural genes of two leaderless bacteriocins weissellicin Y and weissellicin M produced by *Weissella hellenica* QU 13 are located in the same locus [47]. The structural genes of multi-peptides leaderless bacteriocins are co-transcribed. For instance, there is only one promoter has been detected upstream of the ddA gene, and a clear processing site motif of 48 bp was detected between the ddB and ddC genes [44]. The genes responsible for regulation were only found in the biosynthetic gene cluster of lacticinQ/Z, whose production was positively regulated by LmqR, a TetR-family transcriptional regulator [48].

The regulation of most leaderless bacteriocins was associated with environmental stimuli. The production of Enterocin L50, Enterocin P, and Enterocin Q by *Enterococcus faecium* L50 was temperature-dependent [49]. The production of

weissellicin Y and weissellicin M by *Weissella hellenica* QU 13 was nutrition-adaptive and thiamine addition decreases weissellicin Y production [50]. Pasteurized milk supplemented with tryptone significantly improved the production of garvicin KS [51].

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