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REVIEW

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Lantibiotics, Class I Bacteriocins from the Genus *Bacillus*

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Antimicrobial peptides exhibit high levels of antimicrobial activity against a broad range of spoilage and pathogenic microorganisms. Compared with bacteriocins produced by lactic acid bacteria, antimicrobial peptides from the genus *Bacillus* have been relatively less recognized despite their broad antimicrobial spectra. These peptides can be classified into two different groups based on whether they are ribosomally (bacteriocins) or nonribosomally (polymyxins and iturins) synthesized. Because of their broad spectra and high activity, antimicrobial peptides from *Bacillus* spp. may have great potential for applications in the food, agricultural, and pharmaceutical industries to prevent or control spoilage and pathogenic microorganisms. In this review, we introduce ribosomally synthesized antimicrobial peptides, the lantibiotic bacteriocins produced by members of *Bacillus*. In addition, the biosynthesis, genetic organization, mode of action, and regulation of subtilin, a well-investigated lantibiotic from *Bacillus subtilis*, are discussed.

Keywords: Antimicrobial peptides, bacteriocins, lantibiotics, ribosomally synthesized, *Bacillus*

Antimicrobial peptides have been found in most living organisms: prokaryotes, plants, and animals including vertebrates and invertebrates [15, 35, 61]. They have diverse chemical structures and play crucial roles in the innate immunity of early defense systems to protect their hosts from invading pathogens [65]. Among them, a great variety of the peptides are produced by bacteria.. Individual bacteria are subject to competition with either phylogenetically unrelated or closely related microorganisms to survive under limited nutritional conditions. Consequently, antimicrobial peptides, which are indispensible as a component of defensive mechanisms to protect the producers themselves so they may outgrow their competitors, have been extensively investigated [43, 47, 52]. Bacteria produce two different types of antimicrobial peptides that are classified based on biosynthetic mechanisms: ribosomally synthesized peptides, or bacteriocins, that exhibit a relatively narrow range of antimicrobial activity, mainly inhibiting closely related bacteria [20, 43]; and nonribosomally synthesized peptides showing broader spectra of activities, inhibiting bacteria [59] or fungi [36]. The bacteriocins are grouped into four classes (I–IV) based on their biochemical and genetic properties [24]. Both class I and II bacteriocins are small (3–10 kDa), cationic, amphiphilic, membrane-active peptides. Class I bacteriocins, or lantibiotics, contain the unusual amino acids lanthionine and methyllanthionine. In contrast, class II bacteriocins do not contain these modified amino acids. They can be subdivided into three groups: (i) class IIa, *Listeria*-active peptides with the consensus sequence -Y-G-N-G-V-X-C- near the N-terminus; (ii) class IIb, two-peptide bacteriocins in which both components are required for antimicrobial activity; and (iii) class IIc, thiol-activated peptides requiring reduced cysteine residues for activity. Class III bacteriocins are high molecular mass (>30 kDa), heat-labile proteins. Class IV bacteriocins are complex peptides containing lipid or carbohydrate moieties essential for activity.

Fermented foods have been consumed for millennia all over the world. In western countries, dairy products such as cheese, kefir, and yogurt are beneficial microbial reservoirs that contain various groups of lactic acid bacteria (LAB), a number of which produce bacteriocins exhibiting high levels of antibacterial activity [24]. Nisin, a bacteriocin produced by *Lactococcus lactis* subsp. *lactis* from dairy products, has been extensively investigated and approved for use as a food preservative for more than 40 years in over 50 countries [11, 49]. In Asia, traditional fermented foods made of vegetables or crops such as *kimchi* or *doenjang* have been served as the main daily meal for several millennia. The genus *Bacillus* has been recognized as a major group of microorganisms that contribute to fermentation of soybean-based fermented foods in East Asia [21–23, 34], producing diverse antimicrobial peptides that show not only antibacterial but antifungal activities

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[55]. Members of this genus produce both types of antimicrobial peptides: ribosomally synthesized bacteriocins such as subtilin [4] and subtilosin A [3]; and nonribosomally synthesized peptides including polymyxins [33, 37] and iturins [31, 39]. Therefore, *Bacillus* spp. can produce more diverse antimicrobial peptide structures than LAB, which produce only ribosomally synthesized bacteriocins. However, antimicrobial peptides from *Bacillus* spp. have received less notice as natural beneficial antimicrobial compounds, which are applicable to the food, agricultural, and pharmaceutical industries.

In this review, we summarize the current knowledge regarding lantibiotics, class I bacteriocins produced by members of the genus *Bacillus* exhibiting antimicrobial activity against foodborne pathogens. Moreover, the biosynthetic mechanism, mode of action, genetic organization, and regulation of the class I bacteriocin subtilin are described, and the potential application of antimicrobial peptides in the food, agricultural, and pharmaceutical industries is discussed.

Bacteriocins: Ribosomally Synthesized Antimicrobial Peptides

Bacteriocins, ribosomally synthesized antimicrobial peptides from bacteria, have been extensively investigated [19]. Bacteriocins typically exhibit their antimicrobial activity against closely related bacteria. Gram-negative bacteria are known to produce colicins and microcins [12, 13, 51]. In Gram-positive bacteria, nisin and subtilin have been the most thoroughly studied [14]. Bacteriocins have been widely studied because they are generally recognized as safe. Bacteriocins are small (3–10 kDa) and are inactivated by conventional proteolytic enzymes. Despite having different spectra of antibacterial activity, most bacteriocins are cationic and amphiphilic, implying that a common mode of action is shared among different types. Bacteriocins from the genus *Bacillus* that have been mainly investigated are subtilin [14, 48] and subtilosin A [41, 66]. In addition, *Bacillus subtilis*, *B. cereus*, *B. thuringiensis*, and other *Bacillus* spp. have been reported to produce a variety of bacteriocins showing a broad range of antibacterial activity against food spoilage and pathogenic microorganisms [2, 6–8, 32, 40, 44–46, 50, 55]. Thus far, all of the bacteriocins from *Bacillus* spp. whose structures have been elucidated are members of class I, with the exception of a class II pediocin-like bacteriocin, coagulin [30]. Here, we focus on subtilin to introduce the genetic locus, mode of action, and regulatory system of class I bacteriocins produced by *Bacillus* spp.

Lantibiotics. Class I bacteriocins, called lantibiotics, contain the unusual amino acids including lanthionine and β-methyllanthionine as well as dehydrated residues formed by enzymatic reaction. Lantibiotics are subjected to posttranslational modification during maturation, resulting in the presence of the modified amino acids in the mature peptide [17]. Class I bacteriocins exhibit antibacterial activity against closely related Gram-positive bacteria but typically do not inhibit Gram-negative bacteria.

Subtilin, the most extensively studied class I bacteriocin produced by members of the genus *Bacillus* [38], is composed of 32 amino acids, eight of which are modified (Fig. 1A). Subtilin is produced by *B. subtilis* ATCC 6633, an endospore-forming bacterium inhibiting a broad range of Gram-positive bacteria including other *Bacillus* and *Listeria* spp. The structure of subtilin is very similar to that of nisin, which has been applied as a food preservative in dairy products including cheese.

Genetic loci for bacteriocin production. The gene cluster for bacteriocin synthesis is composed of structural gene(s) and accessory genes necessary for bacteriocin transport, immunity, regulation, and processing to produce the mature form; bacteriocin producers require additional proteins involved in immunity for self-protection, enzymatic processing, transport, and regulatory systems composed of induction factors, sensor kinases, and response regulators [42, 62]. Bacteriocins are initially synthesized as premature peptides with a leader or signal sequence at the N-terminus. Immunity proteins are required to protect the producers themselves from the activity of their own bacteriocins. Class I bacteriocins are subject to further posttranslational modification to produce the mature peptide form, resulting in the formation of unusual amino acids such as lanthionines and intramolecular disulfide linkage by enzymatic reaction. Dedicated ATP-binding cassette (ABC) transporters, containing hydrophobic membrane spanning motifs, are required for either dual functioning that includes proteolytic activity on the N-terminus and translocation of the peptides (nisin) or bacteriocin transport only (subtilin). After being modified and transported out of producer cells, bacteriocins are enzymatically cleaved to remove the leader sequence; this step yields mature, active subtilin. Transcription of accessory proteins is co-regulated with the production of bacteriocins by a signal transduction system in a cell density-dependent manner, as discussed in a later section.

The subtilin gene cluster is composed of 10 genes, *spaBTCSIFEGRK*, with a total length of approximately 12 kb [54], and four promoters are involved in its transcription (Fig. 1B). The structural gene encoding presubtilin, composed of 56 amino acids, is *spaS*. Presubtilin requires processing, which yields mature, active subtilin containing 32 amino acids. The mature subtilin structure contains one dehydrobutyrine (Dhb) and two dehydroalanine (Dha) residues as well as one *meso*-lanthionine (Ala-S-Ala) and four 3-methyllanthionine (Abu-S-Ala) ring structures. SpaB and SpaC were predicted to be involved in posttranslational modification on the cytosolic side of the membrane [18, 29]. It has been suggested that SpaT is an ABC transporter protein localized on the membrane for export of presubtilin [29], forming a complex with SpaB

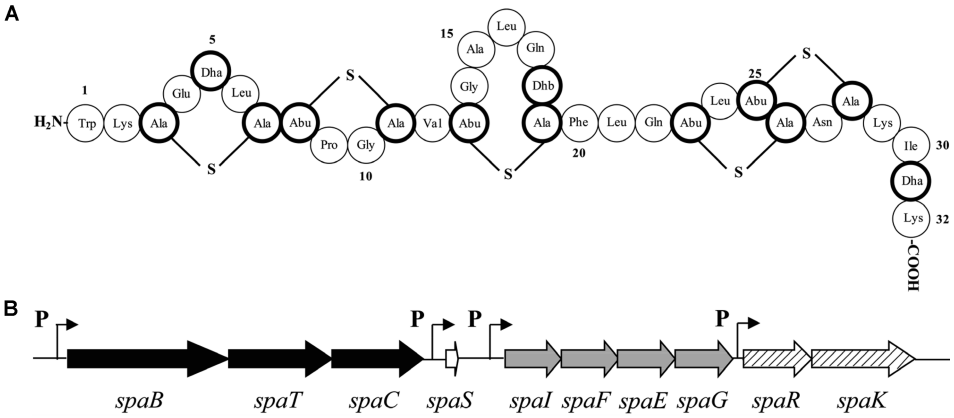

Fig. 1. Subtilin.
A. Schematic representation of the chemical structure of subtilin. One dehydrobutyrine (Dhb), two dehydroalanine (Dha), one *meso*-lanthionine ring (Ala-S-Ala), and four 3-methyllanthionine (Abu-S-Ala) rings are found in the structure. **B**. Genetic organization of subtilin gene cluster. Each capital letter represents a protein involved in subtilin biosynthesis: B and C, precursor modification; T, export; S, structural subtilin precursor; I, F, E, and G, immunity; and R and K, signal transduction. Black arrows represent genes required for posttranslational modification for subtilin maturation; the white arrow is the subtilin structural gene; grey arrows represent immunity-associated genes; and shaded arrows represent regulatory genes. P and bent arrows indicate promoters.

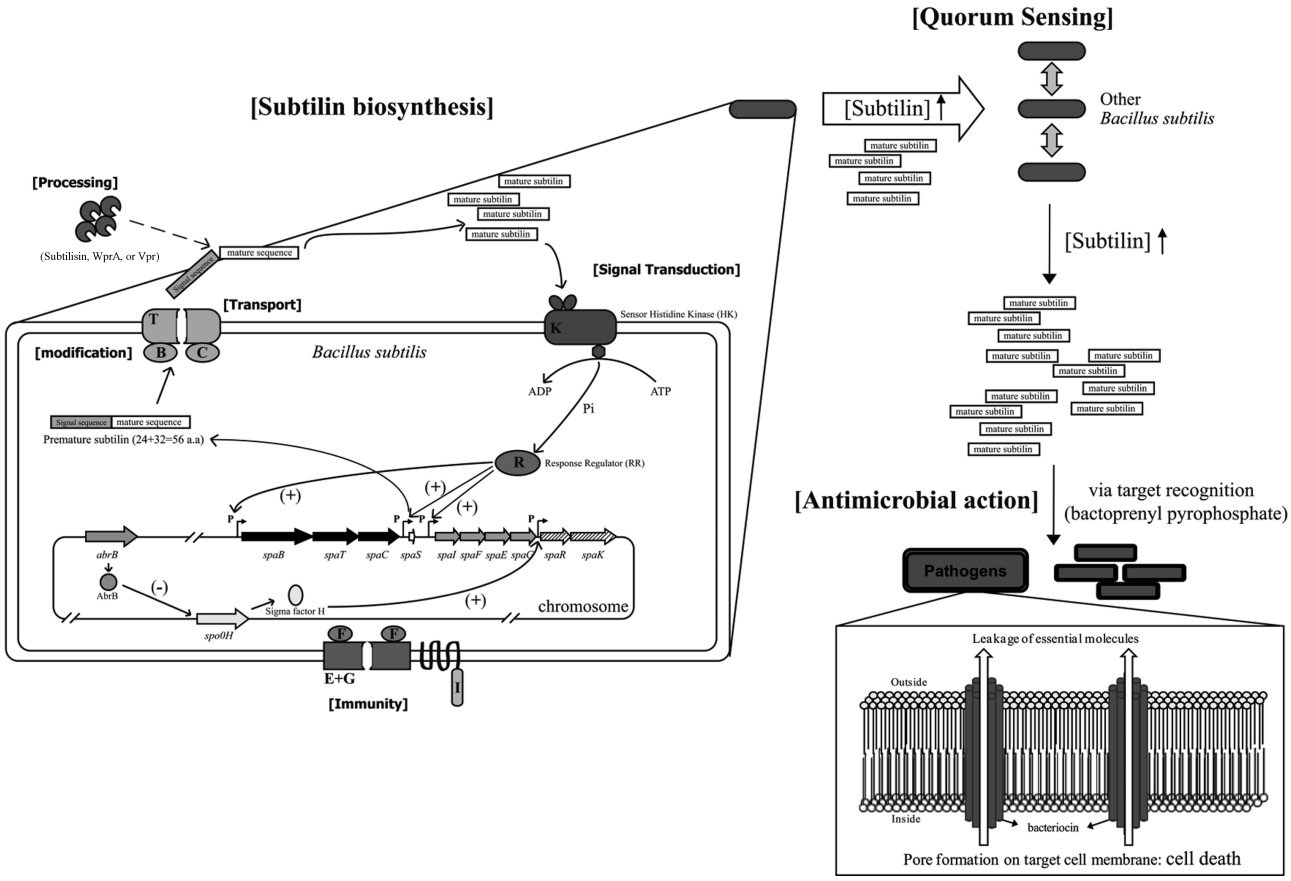

Fig. 2. Schematic representation of subtilin biosynthesis, signal transduction, and regulation in *Bacillus subtilis*; quorum sensing; and antimicrobial action.
Mature subtilin induces its own synthesis; subtilin is recognized by a sensor kinase (SpaK) that subsequently phosphorylates a response regulator (SpaR). The phosphorylated SpaR upregulates three promoters found in the subtilin gene cluster. Sigma factor H under the negative control of AbrB upregulates the *spaR* promoter. Positive and negative signs in brackets indicate up- and downregulation of recognized gene transcription, respectively. When the subtilin concentration reaches a threshold level in the environment, other *B. subtilis* cells are triggered to produce subtilin (quorum sensing). Subtilin exerts its antimicrobial activity by specifically binding to bactoprenyl pyrophosphate in the target cell membrane to form pores that cause leakage of essential molecules, and consequently cell death.

and SpaC; thus, the complex converts presubtilin to modified presubtilin, which contains unusual amino acids and disulfide linkages [53]. After export, modified presubtilin is subjected to proteolytic cleavage by the serine proteases subtilisin (AprE), WprA, and Vpr to form mature subtilin [10]. Four proteins from an operon found in the subtilin gene cluster are involved in the immunity of the producer [9, 28, 57]: SpaI, a membrane-bound lipopeptide presumably responsible for immunity by interacting with subtilin specifically; and SpaF, E, and G, assumed to form a membrane-bound complex where two SpaF molecules are members of the complex on the cytosolic side of the membrane [57]. This complex is expected to be an ABC transporter responsible for pumping subtilin molecules out of producer cells, thus acting as a component of immunity. SpaR and K are required for the signal transduction system described in a later section. A schematic drawing of the proteins involved in subtilin biosynthesis is shown in Fig. 2.

Mode of action. Although antimicrobial peptides have been known to employ different mechanisms of action, these involve either binding to genetic materials or interacting with other vital cell components such as the cell wall, membrane, or intracellular organelles [63, 64]. Among the antimicrobial peptides, bacteriocins are known to form pores in target cell membranes [1]. Bacterial cell membranes are mainly composed of negatively charged cardiolipin, phosphatidylglycerol, or phosphatidylserine; therefore, a cationic bacteriocin can be electrostatically attracted to bacterial cell membranes. Although bacteriocin antimicrobial activity relies on pore formation, the spectrum of activity depends on the peptide; this observation implies that specific receptor molecules on the surface of target cells may generate differences in antimicrobial activity. It has been reported that nisin Z, a variant of nisin A, binds to a specific target, the membrane-anchored cell wall precursor lipid II also targeted by vancomycin, a glycopeptide antibiotic [5]. Because of its specificity for lipid II, nisin can exert antimicrobial effects at nanomolar concentrations. Likewise, subtilin has been found to bind a target molecule, bactoprenyl pyrophosphate, to permeabilize the target cell membrane in a lipid II-dependent manner [48] (Fig. 2).

Regulation of bacteriocin production: Two-component regulatory systems. Quorum sensing, or cell-to-cell communication using a variety of inducers, is generally found in bacteria. It is associated with induction of antimicrobial peptides, expression of virulence factors, genetic competence, sporulation, and other physiological events. Two different types of inducers are involved in communication between bacterial cells: lactone analogs in Gram-negative bacteria, and small peptides in Gram-positive bacteria [26].

Different types of bacteriocins produced by Gram-positive bacteria have been known to be induced by themselves or other peptides [26]. Using these induction molecules, a signal transduction system is employed depending on a switch between phosphorylation and dephosphorylation of the sensor kinase [27]. A signal inducer molecule, histidine protein kinase, and a response regulator are involved in the signal transduction systems for bacteriocin production. When the level of an inducer reaches a threshold in the environment, the inducer from a cell can induce other cells, and subsequently the induced cells produce the bacteriocin at a high level in a short period of time (Fig. 2).

The lantibiotics nisin and subtilin have been shown to employ the bacteriocin molecules themselves for induction of the bacteriocin gene clusters as autoinducers in a two-component regulatory system and in a cell-dependent manner [25, 56] (Fig. 2). The gene cluster for subtilin biosynthesis includes two genes required for the regulatory system: *spaR*, encoding a response regulator homologous protein; and *spaK*, a sensor kinase (Fig. 2). It has been suggested that subtilin is sensed by histidine protein kinase (SpaK) and the signal is transferred to the response regulator (RR; SpaR) by phosphorylation [58]; the phosphorylated RR can recognize the binding domain, the *spa*-box on three promoters upstream of the transcriptional units *spaBTC*, *spaS*, and *spaIFEG*, resulting in subtilin production (Fig. 2). The phosphorylated RR is dephosphorylated to reduce transcription levels and consequently bacteriocin production. In addition, subtilin biosynthesis was shown to be strongly inhibited by deletion of sigma factor H, a typical regulator of activities in the late-growth phase, as an alternative sigma factor. Sigma factor H has been shown to positively regulate transcription of *spaR* and *K*. Transcription of sigma factor H was downregulated by the general transition state regulator AbrB; deletion of *abrB* caused increased subtilin production. Therefore, subtilin biosynthesis is under dual control of two independent regulatory systems: autoinduction using subtilin itself and regulation of transcription *via* sigma factor H [56] (Fig. 2).

Concluding Remarks: Application and Significance of Bacteriocins from Foods

Pathogenic microorganisms such as *B. cereus*, *Listeria monocytogenes*, and *Staphylococcus* spp. have caused serious diseases, and consequently considerable economic loss in the food and agricultural industries. Antibiotics have been practically used to treat these pathogens since penicillin G was discovered more than half a century ago. Many different types of antibiotics have been discovered or synthesized to control pathogenic microorganisms. Repetitive use and misuse of antibiotics by the agricultural and pharmaceutical industries have caused the emergence of multidrug-resistant microorganisms, even to the strongest antibiotics currently available [60]; therefore, the rapid development of more effective antimicrobial compounds is required to keep pace with demand [16].

Food-grade bacteria producing antimicrobial peptides may present a greater opportunity for application in the food and agricultural industries. Fermented foods, including yogurt, cheese, *doenjang*, and *kimchi*, have been recognized as beneficial probiotic sources. Fermentation is performed by different types of food-grade microorganisms; consequently their safety in foods has long been guaranteed. LAB, producers of bacteriocins and organic acids, have been well studied as probiotics. Currently, only nisin is approved by the US Food and Drug Administration for application as a natural preservative in food. In contrast, the potential of class I bacteriocins including subtilin from the genus *Bacillus* have been relatively much less recognized, although they have been well investigated as described herein. Moreover, the antimicrobial activity of these bacteriocins against a variety of pathogens is as high as those of nisin and other bacteriocins from LAB. This factor in combination with their broad antimicrobial spectra makes bacteriocins from *Bacillus* spp. promising for application in the food, agricultural, and pharmaceutical industries. Consequently, it may be advantageous to study bacteriocins from *Bacillus* spp. for the development of more efficient, biologically safe antimicrobial compounds to replace those that cause serious side effects and the emergence of antibiotic-resistant pathogens.

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