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REVIEW

Pediocin-like bacteriocins: new perspectives on mechanism of action and immunity

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Abstract This review attempts to analyze the mechanism of action and immunity of class IIa bacteriocins. These peptides are promising alternative food preservatives and they have a great potential application in medical sciences. Class IIa bacteriocins act on the cytoplasmic membrane of Gram-positive cells dissipating the transmembrane electrical potential by forming pores. However, their toxicity and immunity mechanism remains elusive. Here we discuss the role of the mannose phosphotransferase system (man-PTS) as the receptor for class IIa bacteriocins and the influence of the membrane composition on the activity of these antimicrobial peptides. A model that is consistent with experimental results obtained by different researchers involves the non-specific binding of the bacteriocin to the negatively charged membrane of target bacteria. This step would facilitate a specific binding to the receptor protein, altering its functionality and forming an independent pore in which the bacteriocin is inserted in the membrane. An immunity protein could specifically recognize and block the pore. Bacteriocins function in bacterial ecosystems and energetic costs associated with their production are also discussed. Theoretical models based on solid experimental evidence are vital to understand bacteriocins mechanism of action and to promote new technological developments.

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Introduction

Bacteriocins are ribosomally synthesized peptides produced by bacteria of all genera, which have antimicrobial activity on related bacterial species (Cotter et al. 2005; Drider et al. 2006). They have aroused great interest because of their potential application in medical sciences and food industry. The demand for pathogens-free food, more natural, with fewer chemicals has led to the search for alternative food preservatives. Bacteriocins can offer a solution to this problem because they have some advantages such as pH and heat stability, inhibition of food-borne microorganisms at sub-nanomolar concentrations and easy inactivation by intestinal proteases (Drider et al. 2006; Chikindas et al. 2017). In addition, the increasing resistance to common antibiotics is highly worrisome, thus, it has led to the study of alternative antimicrobials, such as bacteriocins and bacteriophages, as a primary concern (Cotter et al. 2013; Orndorff 2016).

Bacteriocins are classified into: (1) class I (modified), which have post-translational modifications, and (2) class II (unmodified or cyclic), which do not have post-translational modifications. Bacteriocins of class II are subdivided into class IIa: pediocin-like linear peptides, which may contain one or two disulfide bridges and a conserved YGXGV region; IIb: two peptides that require a combined action to exert its activity; IIc: cyclic structured bacteriocins and IId: variable group of linear peptides that do not fit into any of the other groups (Nes et al. 1996; Cotter et al. 2013).

Many lactic acid bacteria produce class IIa bacteriocins which have anti-listerial activity. Since they are produced by GRAS organisms (generally recognized as safe), bacteriocins

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have a great potential as antimicrobial agents in food. The successful use of pediocin PA-1 as a bio-preservative in the food industry has promoted the research on the mechanism of action of class IIa bacteriocins (Rodríguez et al. 2002). It should be considered, as an important advantage that class IIa bacteriocins do not undergo further post-translational modifications than the cleavage of a leader peptide from the precursor. For this reason, heterologous expression of linear bacteriocins is less problematic and possibly much more scalable than class I bacteriocins. In fact, many class II bacteriocins have already been successfully produced in bacterial species different from the natural producers. The understanding of the mechanism of action of class IIa bacteriocins is fundamental for the design and development of new variants with biotechnological applications as food biopreservatives or with potential use in the pharmaceutical industry (Acuña et al. 2012). It has been demonstrated that class IIa bacteriocins act on the cytoplasmic membrane of Gram-positive cells dissipating the transmembrane electrical potential, which results in an intracellular ATP depletion. These peptides induce the exit of ions, amino acids and other essential molecules by forming hydrophilic pores in target membranes (Bhunia et al. 1991; Bruno and Montville 1993; Chikindas et al. 1993; Minahk et al. 2000).

Two models have been proposed to explain class IIa bacteriocins mechanism of action: (a) the bacteriocin would bind the receptor leading to an irreversible opening of an intrinsic channel; or (b) the bacteriocin would employ the receptor as a docking molecule to bring the peptide closer to the plasma membrane, allowing subsequent bacteriocin insertion and oligomerization to form a pore (Fig. 1) (Cotter et al. 2005; Drider et al. 2006). This review attempts to reconsider some aspects of class IIa bacteriocins mechanism of action from a new perspective.

The role of the receptor

To date, there is solid evidence that membrane-associated receptors are necessary for the function of class IIa bacteriocins (Chikindas et al. 1993; Venema et al. 1995; Duquesne et al. 2007; Kjos et al. 2009; Cotter et al. 2013). However, the precise role of the receptor protein and the nature of the pore remain to be investigated.

At first, it was assumed that positive charges of class IIa bacteriocins interacted with anionic phospholipids of target cells, allowing the insertion of an amphipathic portion of the bacteriocin in the membrane (Drider et al. 2006). After that, it was proposed that the mannose phosphotransferase system

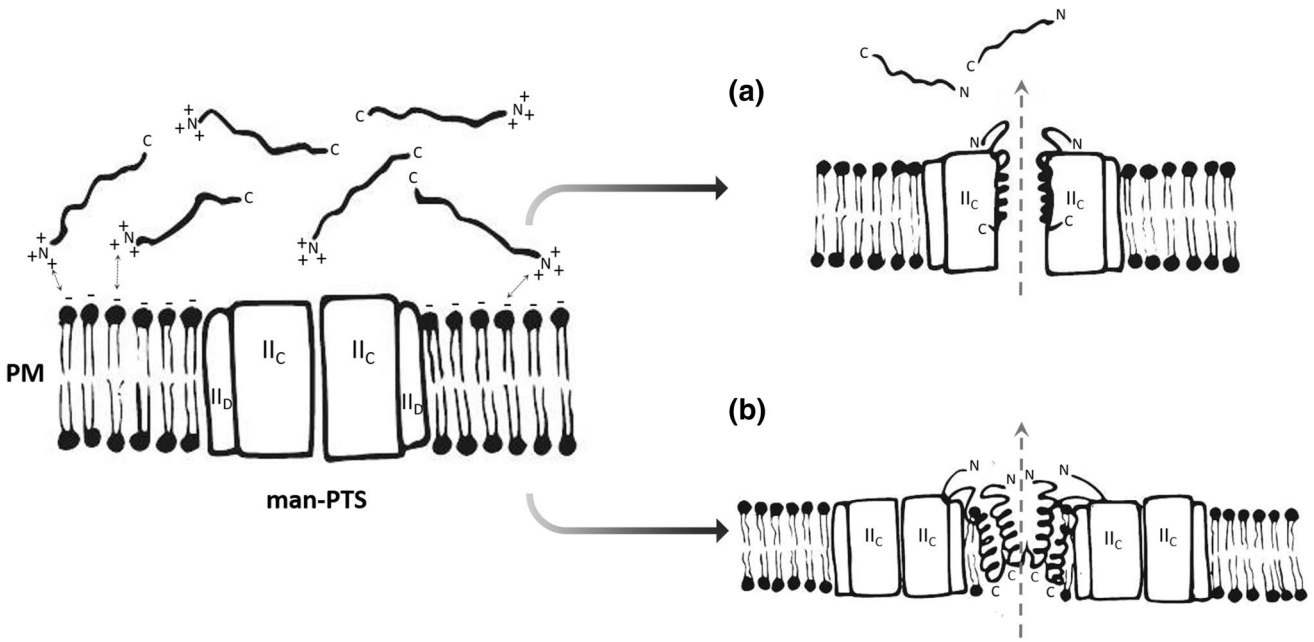

Fig. 1 Proposed models for class IIa bacteriocins mechanism of action. The bacteriocin remains unstructured in the extracellular medium and adopts a well-defined conformation upon contact with the membrane. The positively charged residues in the N-terminal region of the bacteriocin would mediate the initial non-specific binding with the negatively charged phospholipids of the target membrane (left panel). This would lead the peptide from the extracellular medium to the man-PTS receptor to establish an intimate and strong contact. Two models were proposed to explain the subsequent steps: **a** the bacteriocin would induce a conformational change in the receptor leading to an irreversible opening of an intrinsic channel. **b** The bacteriocin would employ the receptor as a docking molecule to bring the peptide closer to the plasma membrane, allowing the following bacteriocin insertion and oligomerization to form a pore. II_C and II_D are the membrane subunits of the man-PTS complex. *PM* plasmatic membrane

(man-PTS) was responsible for *Listeria monocytogenes* sensitivity to class IIa bacteriocins (Ramnath et al. 2000; Dalet et al. 2000, 2001). Eventually, the man-PTS was confirmed as the membrane specific receptor for many pediocin-like bacteriocins (Ramnath et al. 2004). The man-PTS family was phylogenetically clustered into groups I, II and III. Only members from group I seem to function as receptors for class IIa bacteriocins, and the receptor efficiency is directly dependent on their phylogenetic positions (Kjos et al. 2009).

Prior to the consolidation of the man-PTS as the specific receptor for class IIa bacteriocin, there was a preponderant notion that the bacteriocin was capable of permeabilizing the membrane itself. It has been well settled that the flexible hinge between the conserved N-terminal domain and the highly variable C-terminal domain is responsible for the independent function of each region of the bacteriocin (Johnsen et al. 2005b). It was firmly believed that after binding to the membrane of the target cell through the N-terminal region, the C-terminal half penetrated the membrane and interacted with the hydrophobic core playing a major role in determining bacteriocins target cell specificity (Johnsen et al. 2005b). Thus, the composition of the membrane hydrophobic core would be more accurate to determine the antimicrobial spectrum than the functionality of a receptor or docking-site for the peptide on the surface of the cell (Uteng et al. 2003; Haugen et al. 2005).

Pediocin PA-1 was a prime example because it was able to interact directly with lipid vesicles of *L. monocytogenes* permeabilizing the membrane without the need for a receptor protein. So, a receptor was not believed to be essential for pediocin PA-1 activity in vitro, although it was suggested that it might facilitate the post-binding process (Chikindas et al. 1993).

Thereupon, sound evidence was provided of a strong and specific association of the bacteriocin with the man-PTS complex. It was proposed that the N-terminal initially binds to an extracellular loop of the IIC subunit from the man-PTS, whereas the C-terminus might interact with transmembrane segments that entrap the bacteriocin within the receptor. These results support the first mechanism commented above (Fig. 1a) (Diep et al. 2007; Kjos et al. 2010, 2011).

Although evidence over the years appeared to be conflicting to explain pediocin-like bacteriocins mechanism of action, the experimental evidence seems to become reconciled in the second proposed model. There is, indeed, a docking molecule with a key function in the binding and anchoring of the bacteriocin to the membrane. However, the subsequent step might be a receptor-independent interaction with the lipid bilayer, responsible for membrane disruption (Fig. 1b).

Recently, a more conclusive evidence that the man-PTS would participate as a docking molecule, but not as a pore-forming structure was provided by the use of hybrid proteins called "suicide probes" (Gérard et al. 2004). *Escherichia coli* is naturally insensitive to class IIa bacteriocins because they are not able to cross the outer membrane (Stevens et al. 1991; Chalón et al. 2012) and *E. coli* man-PTSs, belonging to group II and III, do not serve as specific receptors (Kjos et al. 2009). Nevertheless, it was proven that if the bacteriocin is anchored to the inner membrane through the bitopic membrane protein EtpM, the bacteria depolarize and die even in the absence of the specific receptor (Barraza et al. 2017). These results suggest that the binding and anchoring of the bacteriocin to the membrane seem to be a sufficient condition for its insertion and pore formation.

Bacteriocin structure

Many details of the structure–function relationship of class IIa bacteriocins were obtained when the three-dimensional structures of leucocin A, carnobacteriocin B2, sakacin P, and curvacin A were solved. The secondary structure have been well characterized by NMR studies in the presence of lipophilic substances that mimic biological membranes such as solvents (TFE) or membrane anionic phospholipids (DPC micelles) (Fregeau Gallagher et al. 1997; Wang et al. 1999; Uteng et al. 2003; Haugen et al. 2005). Interestingly, class IIa bacteriocins seem to exist as a non-structured form in aqueous solution but adopt a well-defined conformation upon contact with membrane mimetic environments (Fregeau Gallagher et al. 1997; Uteng et al. 2003). This supports the idea of a direct phospholipid–bacteriocin interaction that induces structural changes on the peptide. The described structures share some common qualities. The cationic hydrophilic N-terminal forms an antiparallel β-sheet stabilized by a disulfide bridge and several hydrogen bonds. As the N-terminal is shared among all class IIa bacteriocins, they would bind in a similar manner with the IIC extracellular loop of man-PTS (Kjos et al. 2010). A flexible hinge separates the hydrophobic C-terminal domain containing one or two well-defined α-helices followed by a terminal tail creating a hairpin-like structure (Fig. 2). The hydrophobic/amphiphilic properties of this domain suggest that this portion is highly likely to interact with the phospholipids of the membrane (Drider et al. 2006). As a matter of fact, a water-filled pore model upon bacteriocin membrane insertion has been described as a barrel-stave like pore. This structure consists of a bundle of amphipathic peptide helices forming a hydrophilic inner wall and a hydrophobic outer wall that face the fatty acyl chains of the membrane lipids (Fig. 1b) (Moll et al. 1999).

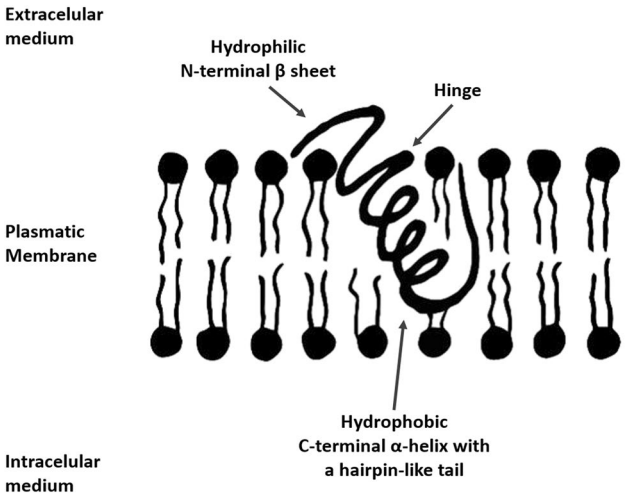

Fig. 2 Proposed model for class IIa bacteriocin secondary structure in the membrane. The cationic hydrophilic N-terminal forms an antiparallel β-sheet that is located at the membrane interface. A flexible hinge separates the hydrophobic C-terminal domain containing one (depicted in figure) or two well-defined α-helices placed on the core of the lipid bilayer. The terminal hairpin-like tail is stabilized by a disulfide bridge or by an interface-localized tryptophan residue (Fimland et al. 2005)

The membrane as a conditioning factor for the mechanism of action

As it was previously mentioned, class IIa bacteriocins act on Gram-positive bacteria, which have a high content of anionic phospholipids in the plasma membrane. Hence, before the description of the man-PTS as the specific receptor, it was raised that the positively charged residues in the N-terminal region of the bacteriocin mediated the initial binding with the negatively charged phospholipids of the membrane (Fig. 1) (Chen et al. 1997, 1998). These electrostatic interactions between the bacteriocin and the phospholipids should still be considered as non-specific bindings that lead the peptide from the extracellular medium to the man-PTS receptor to establish an intimate and strong initial contact. In effect, it was reported that a higher content of negatively charged phospholipids increases the affinity of the bacteriocin for the membrane (Chen et al. 1998).

On the other hand, although genetic down-regulation of the receptor has been reported as a mechanism of resistance against man-PTS targeting bacteriocins (Opsata et al. 2010; Kjos et al. 2011), there are also cases where resistant cells show regular or even elevated man-PTS expression (Vadyvaloo et al. 2002; Tessema et al. 2009; Kjos et al. 2011; Masias et al. 2017). These exceptions illustrate how other features such as membrane lipid composition, fluidity, or cell surface charge might affect and condition bacteriocin-phospholipid interactions, playing an important role in modulating cells sensitivity to the bacteriocin. Actually, it has been proposed that several factors may contribute to the resistance degree. Changes in membrane phospholipid composition seem to explain low-level resistance whereas mutation or lack of expression of the man-PTS complex would determine high-level resistance to class IIa bacteriocins (Vadyvaloo et al. 2002, 2004; Masias et al. 2017).

The immunity mechanism

Bacteriocin-producing cells are protected from the lethal effect of their own bacteriocin by the expression of an immunity protein (Fimland et al. 2002). In general, the immunity protein acts specifically toward its related bacteriocin. A well experimentally supported immunity model suggests that the bacteriocin gets locked onto the receptor by its immunity protein forming a ternary complex, which is settled only when the bacteriocin acts from the outside. Thereby, the immunity protein might interrupt the subsequent steps that lead to cell death (Diep et al. 2007).

The use of hybrid immunity proteins that vary their C-terminal half revealed that this region is involved in specific recognition of their related bacteriocins (Johnsen et al. 2005a). Thus, it was suggested that the C-terminal part of the immunity protein interacts with the C-terminal domain of class IIa bacteriocins (the one that is highly variable and defines the antimicrobial spectrum) through a direct or indirect interaction (Sprules et al. 2004; Johnsen et al. 2005a). Though it has not been possible to demonstrate a direct contact between the immunity protein and the bacteriocin in vitro (Nissen-Meyer et al. 1993; Quadri et al. 1995; Venema et al. 1995), this kind of interaction cannot be ruled out. It is possible that a direct bound occur once the bacteriocin penetrates the membrane and adopts its secondary structure (Fregeau Gallagher et al. 1997). A significant finding that highlights this concept is how the co-expression of enterocin CRL35 immunity protein (MunC) together with the EtpM-Ent35 suicide probe counteracts the lethal effect of the bacteriocin, even in the absence of the specific receptor. Apparently, MunC obstructs the pore in this condition (Barraza et al. 2017). This result suggests that there is indeed, a direct bacteriocin- immunity protein interaction in a membrane-inserted form. The fact that the immunity protein acts only if the bacteriocin is present, supports this conclusion. Because the immunity protein has mostly a cytoplasmic location, it could only get contact with the bacteriocin once the peptide has passed through the membrane. Therefore, in this model of immunity, the pore should be already formed to allow the bacteriocin-immunity protein interaction.

Is there an only target for bacteriocins? Which is the main one?

It seems to be clear that class IIa bacteriocins are pore-forming peptides and that they cause cell death by membrane perturbation. Nevertheless, some studies reveal that they might compromise cellular viability by blocking sugars uptake, because of its interaction with man-PTS. It is reasonable to ask whether the structure or sugar transport functionality of the man-PTS is altered when it is interacting with the bacteriocin or the immunity protein. Indeed, a fitness cost comes along with immunity. Immune cells growth, with mannose or glucose as sole carbohydrate source, is in effect perturbed in the presence of the bacteriocin since the man-PTS is a key pathway for the uptake of these sugars (Diep et al. 2007). It has been previously pointed out that class IIa bacteriocins are capable of binding and kill target cells expressing man-PTS of group I. The fact that, in general, bacteriocins have a reduced spectrum of action, which is restricted to bacterial genera phylogenetically related to the producer strain, support the idea of an alternative purpose for bacteriocins beyond their antimicrobial activity. The role of antimicrobial peptides in bacterial ecosystems has not yet been fully elucidated (Riley and Gordon 1999; Riley and Wertz 2002). The most accepted theory is that they would attack other bacteria that compete directly with the producer bacteria for space within a particular ecological niche. Clearly, this is the most evident role and it has been recently demonstrated for some bacteriocins (Kommineni et al. 2015; Sassone-Corsi et al. 2016). However, the production of the bacteriocin and the immunity protein has demonstrated to imply an energetic cost that compromises bacterial growth in the environment. Notably, the regulation of bacteriocin expression is under control of growth phase and/or quorum sensing showing a finely concerted production mechanism according to the needs of the producing bacterium (Diep et al. 1995; Riley and Wertz 2002; van der Ploeg 2005; Shanker and Federle 2017). It is likely that different types of known bacteriocins have different functions or even that a single bacteriocin has several distinct functions in a bacterial community, and some may even mediate quorum sensing phenomena (Miller and Bassler 2001).

Conclusion

Through the years, different mechanisms have been proposed to explain class IIa bacteriocins toxicity and immunity. Regarding the role of man-PTS, there is no doubt that its presence is necessary to render a target sensitive, and it is a required condition for bacteriocins anchoring to the membrane. Nonetheless, as we have previously underlined, many studies support the model in which the bacteriocin is able to disrupt a membrane itself, although a significantly higher peptide concentration is necessary (Drider et al. 2006). The influence of the membrane composition on bacteriocins activity cannot be denied and it could be a key factor in the proper bacteriocin insertion and the final step of pore formation. Based on the results presented to date by several authors, we believed that the second proposed model, in which the pore is formed by the bacteriocin attached to the receptor, would be more accurate to explain the mechanism of action and immunity of bacteriocins. In respect of immunity process, though no direct in vitro interaction has been reported, an in vivo system provided sound evidence that immunity protein might bind the bacteriocin, not in aqueous solution but in a membrane-inserted conformation.

This issue remains to be investigated and a complete elucidation of the molecular basis of these peptides is essential to engineer broad-spectrum bacteriocins that could bind to ubiquitous bacterial membrane components others than the specific receptor.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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