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ORIGINAL ARTICLE

Properties of *Listeria monocytogenes* on Acquisition of Pediocin Resistance

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Abstract

A class IIa bacteriocin pediocin can be used in food biopreservation due to its high activity against foodborne pathogens, such as *Listeria monocytogenes*. In this study, pediocin-resistant *L. monocytogenes* variants were generated, and different properties of the mutants were compared with wild-type *L. monocytogenes*. Bacteriocin-resistant *Listeria* variants were selected on BHI agar containing pediocin. Susceptibility of *Listeria* strains to different bacteriocins and antibiotics were tested by agar well diffusion method. Growth properties were monitored by recording absorbance at 600 nm. Changes in cell properties were evaluated by determining cell surface hydrophobicity and adsorption of pediocin onto *Listeria* cells. Transcriptional levels of *mptA* gene in wild-type and mutant strains were quantified by real-time PCR. Mutations in DNA were examined by sequencing. The two stable resistant variants were less sensitive also to class IIa bacteriocins, but not to nisin and ampicillin. In BHI broth supplemented with glucose or mannose, the wild-type strain grew faster than the resistant variants, whereas with cellobiose, the mutants grew better. The bacteriocin-resistant cells showed increased hydrophobicity, as well as lower adsorption of pediocin on cell surface than wild-type *Listeria*. Significant downregulation of *mptA* gene was observed in Lmo-r2 variant but not in Lmo-r5 variant. However, no mutations in the regulatory genes *resD* and *lmo0095* of the variants were observed, and only minor changes were found in upstream region of the *mpt* operon. These results demonstrated differences in growth, carbohydrate utilization, cell surface, and gene transcription between wild-type and pediocin-resistant strains. This makes it evident that bacteria can use various and complex ways to acquire resistance to antimicrobial compounds.

Keywords *Listeria monocytogenes* · Pediocin · Resistance · Antimicrobial activity

Introduction

Listeria monocytogenes is a foodborne opportunistic pathogen with the ability to survive in a variety of foods and grow in a wide range of pH values, low water activity, high salt conditions, and low temperatures (Paul et al. 2014; Hyden et al. 2016). This pathogen is responsible for outbreaks of listeriosis, causing high mortality rate and great public concern especially in ready-to-eat food products. Meanwhile, consumers' increasing demand for green, natural, and minimally processed foods take challenge for food biopreservation. Bacteriocins produced by food grade microorganisms such as lactic acid bacteria (LAB) are promising options to be used for biopreservation in food industry. LAB bacteriocins have various advantageous properties including inhibition of pathogenic and spoilage microorganisms and causing little, if any, off-flavor or textural changes in foods (Garsa et al. 2014). Bacteriocins are ribosomally synthesized antimicrobial peptides or proteins, which can be divided into several different classes. Bacteriocins in class IIa heat stable unmodified peptides contain a consensus sequence YGNGV, so-called pediocin box, and showing high activity against *L. monocytogenes* (Cotter et al. 2005; Umu et al. 2016). Pediocin produced by *Pediococcus acidilactici* is the

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representative of class IIa bacteriocins. The fermentation product of *P. acidilactici* named ALTA™2341 aimed to be used in food biopreservation, has shown strong antimicrobial activity in meat and cheese products during their storage (Porto et al. 2017).

Applying bacteriocins as biopreservatives raises concern about the emergence of bacteriocin-resistant mutant strains. Studies have revealed that foodborne microorganisms can develop resistance against cationic antimicrobial peptides (CAMPs), such as class IIa bacteriocins (Lather et al. 2015). With exposure to sublethal concentrations of class IIa bacteriocins, susceptible strains may acquire resistance with different levels in frequency and stability (Gravesen et al. 2002a; Tessema et al. 2009). It has been shown that decreased expression of *mptACD* (mannose permease two) operon can be one of the causes for acquired resistance against class IIa bacteriocins, although the specific role in the levels of sensitivities has not been fully illustrated (Kjos et al. 2011; Tessema et al. 2011). In addition, the *mpo* (mannose permease one) operon, the *rpoN* gene encoding the σ54 factor, the *manR* gene encoding the transcriptional activator for σ54, and alteration of cell wall features have also been reported to be involved in resistance to class IIa bacteriocins (Robichon et al. 1997; Dalet et al. 2003; Arous et al. 2004; Vadyvaloo et al. 2004a). Since limited information has been known about the receptors to which bacteriocins target cells bind (Cotter 2014), better understanding of the resistance mechanism may help in elucidating the interaction between bacteriocin and receptors and developing novel antimicrobial peptide for coping with resistant strains.

In the present study, pediocin-resistant (ped^r) *L. monocytogenes* variants were generated and further examined for their characteristics. The physiological changes observed in the variants were compared with wild-type *Listeria*.

Materials and methods

Bacterial strains and culture conditions

The wild-type *L. monocytogenes* ATCC 15313 (Lmo) and resistant derivatives were grown in Brain Heart Infusion (BHI) broth at 37 °C. Pediocin-producing strain *P. acidilactici* PA003 was cultivated in MRS broth at 37 °C for 16 h. Another two class IIa bacteriocin-producing strains *Lactobacillus curvatus* ATCC 51436 and *Lb. plantarum* CICC 24194 were cultured in MRS broth at 28 and 37 °C for 16 h, respectively.

Bacteriocin preparation and activity assay

Culture of *P. acidilactici* PA003 was used to purify pediocin according to the method of Wang et al. (2015). Cell-free culture supernatants (CFSs) of bacteriocin-producing cells were obtained by centrifugation of over-night culture at 7000×*g* for 10 min. Before filtration through 0.22 μm membrane filter (Millipore), pH was adjusted to 7.0 with NaOH. Bacteriocin activity was determined by using the agar well diffusion method (Liu et al. 2011). One arbitrary unit (AU) was defined as the reciprocal of the highest dilution that shows clear inhibition of the indicator zone. The total AUs per milliliter were calculated by $2^n \times (1000/x)$, where n is the number of wells showing clear inhibition; x is the bacteriocin volume in each well.

Selection of induced ped^r strains of *L. monocytogenes* and susceptibility test

L. monocytogenes was cultured by spreading on BHI agar containing 50 AU/mL pediocin. Small colonies appearing on the plate were picked and streaked on BHI agar containing 100 AU/mL pediocin, from which the colonies were streaked on BHI agar with 200 AU/mL pediocin, in order to get single ped^r colonies. Two spontaneous ped^r variants were picked and designated as Lmo-r2 and Lmo-r5. The stabilities of the resistance of the mutants were tested by serial cultivation for 10 subcultures in the absence of pediocin. The susceptibilities of the wild-type *L. monocytogenes* and resistant variants to different bacteriocins and antibiotics were tested by agar well diffusion method. For determination of the minimum inhibitory concentration (MIC), samples were added after series double dilutions. The MIC was defined as the lowest concentration of sample that induced a clear inhibition zone.

Growth properties

BHI broth supplemented with different sugars (1% wt/vol glucose, mannose and cellobiose) and different activities of pediocin (50 and 100 AU/mL) were prepared. Into these media, wild-type *Listeria* and its two ped^r variants from BHI broth cultures were added with 1‰ inoculation, and the growth was monitored by recording absorbance at 600 nm using a microplate spectrophotometer (Infinite 200, Tecan, USA). Plain cultures without inoculation were used as control.

Table 1 Primers used for qRT-PCR

Primer	Sequence (5′-3′)
16S rRNA-F	CGTGCTACAATGGATAGTA
16S rRNA-R	CTACAATCCGAACTGAGAA
mptA-F	TGGCTCACTCTGTAGGTA
mptA-R	TTAGGGACTTTACGCACAT

Table 2 Primers used for sequencing

Primer	Sequence (5′-3′)
mptApro-F	AAATGACTTTTTTAGAATTC CATCAA
mptApro-R	GATTGCTTTAACGTTTTCTTGC
lmo0095-F	AAATGACTTTTTTAGAATTC CATCAA
lmo0095-R	TCTATTTTAAGCACAAGATGCCT
resD-F	TGAGTACTTATGAGTGAACAAGT
resD-R	CTTAGTCTGTTTTATTAATCTTCTG

Cell surface hydrophobicity

L. monocytogenes cells were cultured in BHI broth at 37 °C over-night and centrifuged at 7000×*g* for 10 min. Cells were washed three times in 50 mM phosphate buffer (pH 6.5) and adjusted to $OD_{600\ nm}$ of 0.5. A 4.8 mL cell suspension was mixed with 0.8 mL of xylene and vigorously shaken for 1 min. After 45 min at room temperature, the aqueous phase was carefully removed and determined the $OD_{600\ nm.}$ The cell surface hydrophobicity was measured as the percentage of adherence as adherence (%) = $(1\text{-}A/A_0) \times 100$, where A_0 and A are the $OD_{600\ nm}$ of the cell suspension before and after mixing with xylene, respectively (Pérez et al. 1998).

Adsorption of pediocin on indicator cells

Both wild-type and resistant cells were cultured in BHI overnight and then centrifuged at 7000×*g* for 10 min. Cells were washed with PBS three times and resuspended to 10^8 cfu/mL in the same buffer containing 320 AU/mL pediocin. After incubation at 30 °C for 1 h, supernatant was obtained by centrifugation at 7000×*g* for 10 min and tested the titer of pediocin activity by agar well diffusion method. PBS containing 320 AU/mL pediocin without cells was used as control.

Inactivation of bacteriocins by secreted enzymes

Both wild-type and resistant cells were cultured in BHI broth before centrifugation at 7000×*g* for 10 min, and CFSs of *Listeria* strains were mixed with pediocin. After incubation at 30 °C, bacteriocin titers were tested at different intervals and BHI broth mixed with pediocin was used as control.

Sensitivity to lysozyme action

The experiment was carried out according to Mehla and Sood (2011). The wild-type strain and Ped^r variants were cultivated in BHI at 37 °C overnight. Cells were then inoculated into fresh BHI broth containing lysozyme at 4 mg/ml with $OD_{600\ nm}$ of approx. 0.1 and incubated at 37 °C for 3 h. The absorbance at 600 nm wavelength was read. Cells inoculated into BHI broth without lysozyme were used as control.

RNA isolation, cDNA synthesis, and qRT-PCR analysis

L. monocytogenes wild-type cells and ped^r variants were cultured in BHI broth to approx. $OD_{600\ nm}$ attained 0.5. Cells were harvested by centrifugation and washed with sterilized distilled water. RNA of cells was isolated using Bacterial Total RNA Extraction Kit (cat. no. A010700, Apex, Beijing) according to the manufacture's instruction. RNA concentration was determined by UV-Visible spectrophotometer (Colibri, Titertek-Berthold, Germany) before cDNA synthesis using the iScript™ cDNA Synthesis Kit (cat. no. 170-8891, Bio-rad, USA). Primers designed are listed in Table 1. Quantitative real-time reverse transcriptase PCR (qRT-PCR) experiment was performed using Taq SYBR® Green qPCR Premix (cat. no. EG15135, Yugong Biolabs, Lianyungang, China) to quantify the transcriptional level of *mptA* gene, using 16S rRNA as a house-keeping gene.

DNA amplification and sequencing

Listeria genome DNA was extracted using a bacterial genome DNA extraction kit (cat. no. GK1071, Generay, Shanghai, China). The *mptA* promoter region was amplified and sequenced using primers mptApro-F and mptApro-R. *lmo0095* gene was amplified and sequenced using primers lmo0095-F and lmo0095-R. *resD* gene was amplified and sequenced using primers resD-F and resD-R. Primer sequences are listed in Table 2.

Table 3 Susceptibility of wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5) to class IIa bacteriocins

Indicator strain	CFS of *P. acidilactici* PA003 (AU/mL)	CFS of *Lb. curvatus* ATCC 51436 (AU/mL)	CFS of *Lb. plantarum* CICC 24194 (AU/mL)	Pediocin (AU/mL)
Lmo	320	160	160	1280
Lmo-r2	ND	ND	ND	640
Lmo-r5	ND	ND	ND	640

ND not determined

Table 4 MICs of nisin and antibiotics to wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5)

Indicator strain	Nisin (μg/mL)	Kanamycin (μg/mL)	Ampicillin (μg/mL)
Lmo	625	6.25	12.5
Lmo-r2	625	3.13	12.5
Lmo-r5	625	6.25	12.5

Statistical analysis

Experiments were performed using three independent series. The data reported are the means of three repetitions. Results with $p < 0.05$ were considered significant.

Results and discussion

Selection and susceptibility of ped^r mutants of *L. monocytogenes*

Nisin resistance can be acquired by repeated exposure of sensitive strains to increasing nisin concentrations (Ming and Daeschel 1993; Garde et al. 2004). In this study, ped^r mutants were generated by serial cultivation of *L. monocytogenes* cells in gradual increasing pediocin concentrations (50, 100, and 200 AU/mL). Two stable mutants growing on plates containing 200 AU/mL pediocin were picked after 24 h incubation, designated as Lmo-r2 and Lmo-r5, and tested for susceptibility to different bacteriocins and antibiotics (Tables 3 and 4). Wild-type *Listeria* strain was sensitive to all the tested samples. Purified pediocin attained 1280 AU/mL and was more effective against the wild-type strain than the variants. The antimicrobial activities of CFSs from *P. acidilactici* PA003 (pediocin), *Lb. curvatus* ATCC 51436 (curvacin A) and *Lb. plantarum* CICC 24194 (unknown class IIa bacteriocin) were 320, 160, and 160 AU/mL, respectively, to wild-type *Listeria*. In contrast, the CFSs from bacteriocin-producing strains did not inhibit the ped^r variants at all. In other words, pediocin-induced resistance provides resistance to other class IIa bacteriocins. Similar results have also been reported before. For instance, *Leuconostoc pseudomesenteroides* strain made resistant to class IIa bacteriocin leucocin C, showed resistance also to other class IIa bacteriocins leucocin A and pediocin (Wan et al. 2015). All these bacteriocins target the same receptor on cell surface, namely, the mannose phosphotransferase (Man-PTS). Thus, the mechanism for the bacteriocin resistance could depend on the Man-PTS, and its expression, function, availability, or mutations. The susceptibilities to nisin and antibiotics of the wild-type and the variants were the same, except variant Lmo-r2 was more sensitive to kanamycin. Martínez and Rodríguez (2005) reported the nisin-resistant strains were more susceptible to the antibiotics than their wild-type strains probably because of fitness cost associated to development of nisin resistance.

Growth properties of wild-type and ped^r strains in different conditions

The growth of wild-type *Listeria* and the two variants in different culture conditions was examined. In plain BHI broth, the wild-type *L. monocytogenes* grew faster than the Ped^r variants, reaching stationary stage approximately at 10 h (Fig. 1a). However, resistant variants reached higher cell density after 12 h cultivation, which, in fact, is in accordance with previously reported findings about nisin-resistant *L. monocytogenes* reaching higher optical density than the wild-type strain (Crandall and Montville 1998). When pediocin was added into BHI broth to final concentrations of 50 and 100 AU/mL, wild-type *Listeria* did not grow within 12 h, as shown in Fig. 1b. Resistant variants Lmo-r2 and Lmo-r5 showed similar growth patterns in presence of pediocin, reaching lower final optical density with the increasing of pediocin concentration. With different carbohydrate sources,

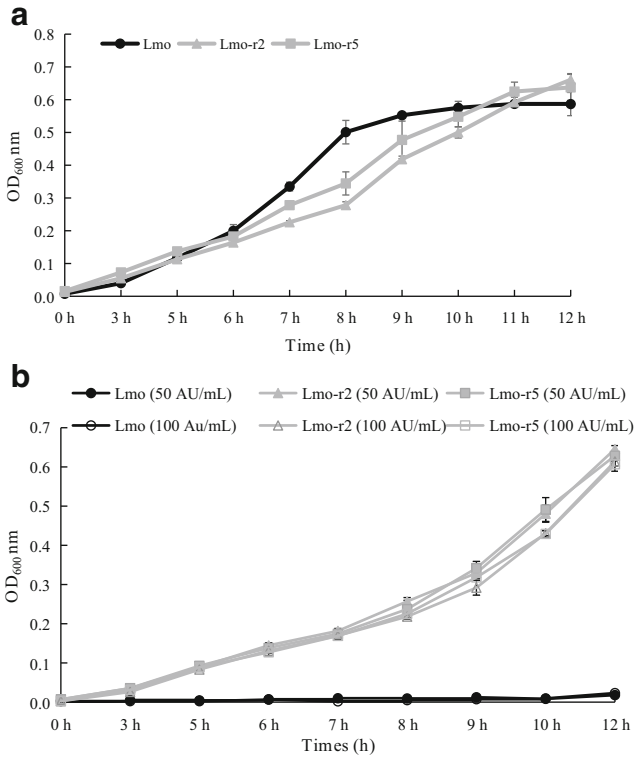

Fig. 1 Growth curves of wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5) in BHI broth (**a**) and BHI broth containing 50 AU/mL and 100 AU/mL pediocin (**b**)

the variants also showed similar growth patterns (Fig. 2a–c). With glucose or mannose, the wild-type strain grew slightly faster attaining stationary phase about 1 h earlier than the variants. Interestingly, when cellobiose was added, resistant variants exhibited higher optical densities in exponential phase than the wild type. The differences in growth between the wild-type and the resistant mutants with different carbohydrates indicate that sugar metabolism pathways, or their preferred use, may have been altered in the resistant strains. Similar phenomenon has also been observed before. According to Vadyvaloo et al. (2004b), studies indicated that wild-type strains had a higher growth rate in the presence of glucose, while the class IIa bacteriocin-resistant strains grew faster in the absence of glucose. Kjos et al. (2011) also reported a shift in sugar metabolism in bacteriocin-resistant mutants exhibiting reduced growth on glucose but improved growth on galactose.

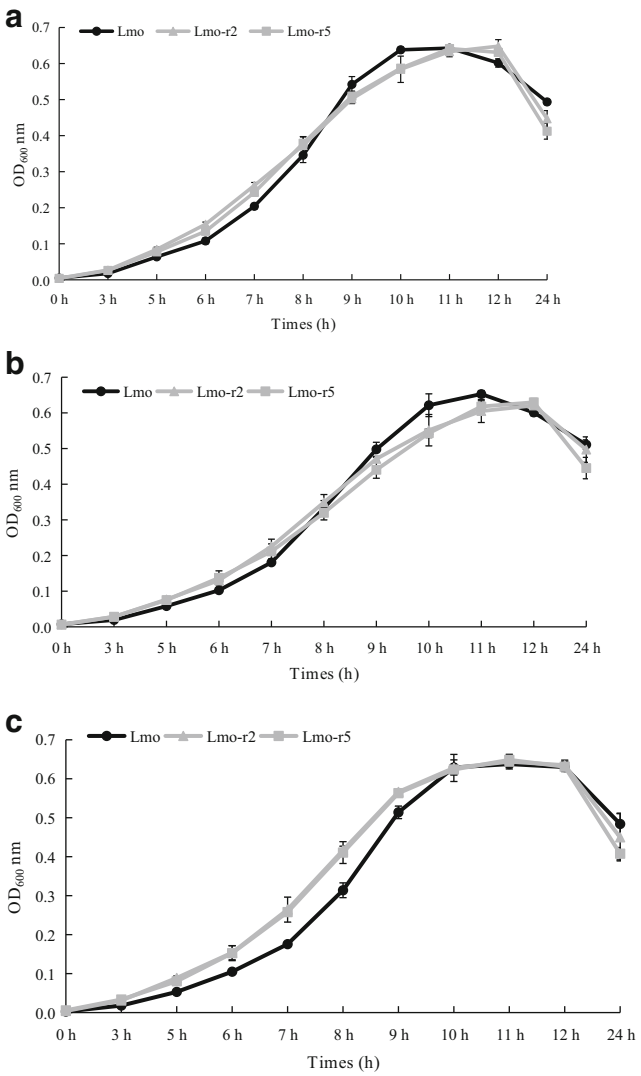

Fig. 2 Growth curves of wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5) in BHI broth added with 1% glucose (**a**), mannose (**b**), and cellobiose (**c**)

Different features in cell surface hydrophobicity

The cell surface of bacteriocin-resistant mutants, for instance *Enterococcus faecalis*, has been reported to be more hydrophobic than the surface of sensitive wild-type cells (Kumariya et al. 2015). Therefore, the next aim in our study was to determine whether the hydrophobicity of the surface of the ped^r *Listeria* cells had also changed. Cells suspensions were treated with xylene, and the proportions of the cells in aqueous phase were determined. As shown in Fig. 3, cell surface of both resistant variants showed increased hydrophobicity. Significant differences in cell counts in aqueous phases were observed between wild-type *Listeria* and ped^r Lmo-r2 ($p < 0.01$) or Lmo-r5 strain ($p < 0.05$). Increase in cell surface hydrophobicity can be interpreted as the likelihood to form cell aggregates as a survival strategy (Mehla and Sood 2011). A thickened cell wall and increased cell wall hydrophobicity were detected in the nisin-resistant *Listeria innocua* variants (Maisnier-Patin and Richard 1996). Likewise, nisin-resistant *L. monocytogenes* Lm41 was found to be more hydrophobic than the corresponding wild-type strain (Martínez and Rodríguez 2005). On the other hand, Kaur et al. (2014) showed that ped^r *L. monocytogenes* MTCC 657 strain was less hydrophobic than the wild-type counterpart, while resistant *L. monocytogenes* ATCC 53135 strain was more hydrophobic than the wild one. Thus, the changes in the architecture of cell surface are probably results of different actions and triggered by different mechanisms according to strain specificities.

Adsorption of pediocin on indicator cells changes

Previous research suggested enterocin CRL35-resistant *Listeria* strains were able to bind enterocin CRL35, although to a lesser extent (Masias et al. 2017). In order to further investigate if *Listeria* strains interact differently with pediocin, *Listeria* cells were exposed to pediocin in PBS and measuring the pediocin concentration in the buffer after the exposure. The results in Table 5 showed that resistant *Listeria* adsorbed less pediocin compared to the wild one. Class IIa bacteriocins

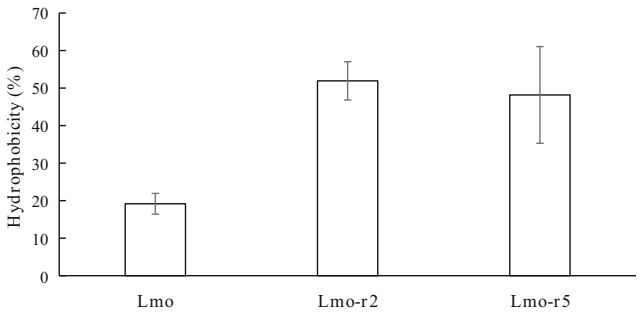

Fig. 3 Hydrophobicity of wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5)

Table 5 Pediocin activities in PBS after mixing with wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5) cells

Strain	Activity (AU/ml)
Lmo	80
Lmo-r2	160
Lmo-r5	160
Control	320

are CAMPs, and thus electrostatic interactions with cell surface play critical role in their binding to the cells. It seems possible that the observed more hydrophobic cell surface is less suitable for pediocin binding. Alternatively, the weaker pediocin binding may be a result of a mutation in the receptor Man-PTS, or its reduced expression level, as reported by Kjos et al. (2011).

Examination of inactivating pediocin by extracellular enzymes

Several researches noted that nisin resistance was conferred by the enzyme nisinase which neutralize antimicrobial activity of nisin observed in *Bacillus* species, *Streptococcus thermophilus*, and *Lb. plantarum* (Zhou et al. 2014). We tested both wild-type and resistant *Listeria* strains for their pediocin-degrading activity. Results in Table 6 revealed that none of the strains inactivated pediocin. It can be concluded that the observed pediocin resistance is not based on secreted proteases or other enzymes, destroying the pediocin activity.

Analysis of sensitivity to lysozyme action

As the cell surface was shown to be changed in the ped^r variants, the effects of lysozyme on growth of *Listeria* strains were then investigated. The lysozyme sensitivity of wild-type strain and Ped^r variants Lmo-r2 and Lmo-r5 was determined by incubating them in the presence of lysozyme for 3 h at 37 °C, after which the growth rates (h^{-1}) were determined. No significant differences could be seen between cells with or without lysozyme treatment (Fig. 4). In previous studies, Kaur et al. (2012) observed that a ped^r *Listeria* variant was more resistant to lysozyme than the wild-type. In another study by Mehla and Sood (2011), in the presence of lysozyme, the

Table 6 Pediocin activities after mixing with wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5) CFSs at different intervals

Time	Control	Lmo	Lmo-r2	Lmo-r5
0.5 h	320	320	320	320
1.5 h	320	320	320	320

Results are given in pediocin activities (AU/mL)

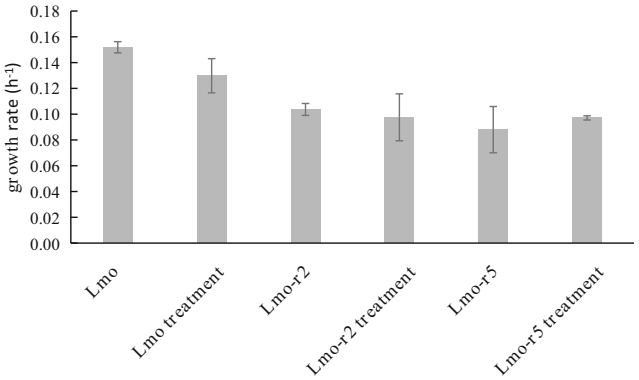

Fig. 4 Growth rates of wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5) with or without lysozyme treatment

growth rates for the wild-type *E. faecalis* and the alamethicin-resistant variants were similar. As also discussed above, it is likely that different kinds of changes in cell surface can cause antimicrobial resistance, and depending on the change, also other phenotypic changes can be developed.

Analysis of *mptA* gene transcription

The Man-PTS is a major sugar uptake system and also certain bacteriocins receptor on sensitive cells. It has been revealed that the specificity of class IIa bacterioicns is dependent on one of the Man-PTS domains, and there is a correlation between the Man-PTS gene expression level and the degree of sensitivity to class IIa bacteriocins (Kjos et al. 2009; Kjos et al. 2010). Previous studies showed that variants resistant to pediocin-like bacteriocins may reduce the expression of Man-PTS (Ramnath et al. 2000; Gravesen et al. 2002b; Opsata et al. 2010). Inactivation of *mptA* gene resulted in a high level of resistance to class IIa bacteriocins (Gravesen et al. 2002b). In this study, the expression level of *mptA* gene in different *Listeria* strains was examined by qRT-PCR. The transcriptional level of *mptA* gene in ped^r mutant Lmo-r2 was downregulated to 0.44-fold compared to the wild type, while the transcriptional level of *mptA* in Lmo-r5 was upregulated

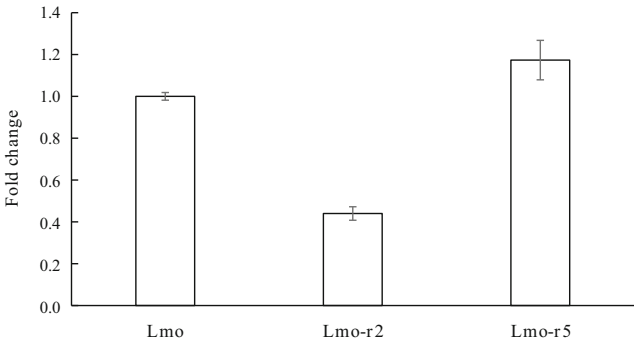

Fig. 5 Changes in *mptA* gene transcription in wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5)

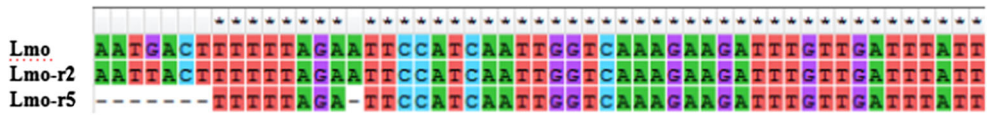

Fig. 6 Identification of *mpt* promoter region in wild-type *L. monocytogenes* (Lmo) and ped^r variants (Lmo-r2 and Lmo-r5)

1.17-fold compared to the wild type (Fig. 5). Therefore, *mptA* gene transcription patterns differed in these two variants, indicating diverse adaptive responses of cells to bacteriocin, a phenomenon that has also been described earlier by Tessema et al. (2009) and Kjos et al. (2011).

Identification of regulatory genes by sequencing

A possible explanation for the bacteriocin resistance is mutations in either receptor or its regulatory genes. Two regulatory genes of carbohydrate metabolism, *resD* (Larsen et al. 2006) and *lmo0095* (Vu-Khac and Miller 2009), were identified and sequenced, as well as the promoter region of the *mptACD* operon. There was no difference between the sequences of *resD* and *lmo0095* in wild-type and the resistant strains (results not shown). For *mptACD* promoter region, only 1 nt change and 1 nt deletion were detected in Lmo-r2 and Lmo-r5, respectively (Fig. 6). However, the mutations were located upstream of the apparent promoter region.

Conclusion

This study presented the acquisition of ped^r trait by exposure of sensitive *L. monocytogenes* cells to gradually increased pediocin concentrations. Mutant cells also gained resistance to other class IIa bacteriocins. Different patterns of carbohydrate utilization, surface hydrophobicity, and transcription levels of a receptor gene were detected in wild-type and resistant variants. Therefore, resistant variants probably use various strategies to protect themselves against antimicrobials. Environmental changes and challenges trigger different responses in metabolic regulation, leading to different cell phenotypes, some of which are useful for the survival in the presence of bacteriocins. Due to the complex and diverse phenotypic changes and multiple responses in resistant variants, systematic research in gene regulation network by using high-throughput technology would be helpful to identify the key mechanism pathways involved in the development of resistance.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals N/A

Informed consent N/A

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