Construction of prcK and prcR Mutant Strains of *Lactobacillus paracasei* HD1.7 and the Impact on the Production of Paracin 1.7

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Abstract

Gene knockouts of *prcK, prcR* and both together were constructed in *L. paracasei* HD1.7. The antimicrobial activities of the *prcK, prcR* and *prcKprcR* mutant strains against *B. subtilis* were 23.6%, 21.9% and 36.6% lower than that of the parental strain, respectively, indicating that these genes affect production of bacteriocin antimicrobial peptides. qRT-PCR assays showed that the relative transcription levels of *prcK* and *prcR* mRNA in the ΔK and ΔR strains were 0.36 and 0.33 times of that in parental bacteria, respectively. Our data suggest that *prcK* and *prcR* are quorum sensing related genes that influence production of the bacteriocin Paracin 1.7. This research provides the basis for exploring the functions of these genes in the production of Paracin 1.7 and more generally for the exploration of the biological preservatives instead of chemical preservatives.

Introduction

Lactobacillus paracasei HD1.7 (CCTCCM 205015) was isolated from Chinese sauerkraut juice in 2003. In previous studies, the fermentation broth of *L. paracasei* HD1.7 contains a type of peptide, Paracin 1.7, a bacteriocin, that could inhibit the growth of several Gram-positive bacteria (G^+), Gram-negative bacteria (G^-) and yeast.[1] The bacterial production process of Paracin 1.7 had characteristics of quorum sensing. Nakayama identified a series of genes in *L. paracasei* E93490 that were assigned as putative quorum sensing components, and predicted that the signaling molecule of *L. paracasei* E93490 might have antibacterial activity.[2] The antibacterial activity may be similar to Paracin 1.7 produced by *L. paracasei* HD1.7.

Quorum sensing in G^+ is regulated by a two-component regulatory system composed of a histidine protein kinase (HPK) and a phosphor-aspartyl response regulator (RR).[3-5] The RR, a DNA binding protein, activates related genes transcription; the phosphorylated RR can bind to the target promoter, directly or indirectly regulating expression of genes.[6] Quorum sensing in *L. paracasei* is not well understood. Putative histidine protein kinase (*prcK*) and response regulator (*prcR*) genes have been identified in *L. paracasei* E93490 by PCR, but functional studies were not conducted.[2] Therefore, in this work, we investigated the functions of the *prcK* and *prcR* genes in quorum sensing and in the potentially related process of the production of antimicrobial peptides.

Gene knockout technology was instrumental in the understanding of quorum sensing.[7-10] Insertional inactivation has been the main method applied to G^+ bacteria.[11] In this method, the flanking sequences of the exogenous DNA imported into host cells and of the target gene in the chromosome of host cells are homologous. The marker gene in the exogenous DNA fragment is therefore inserted into the target gene via homologous recombination, leading to the inactivation of the target gene by the replacement of its DNA.

In this study, we constructed suicide plasmids to create insertional inactivation-based gene knockouts. DNA was incorporated into the chromosome of *L. paracasei* HD1.7 to produce knockouts of *prcK*, *prcR* and *prcKprcR*, with the tetracycline resistance gene used as a marker (replacement DNA) in each case. Growth of colonies on plates containing tetracycline indicated that homologous recombination between the suicide plasmids and the host cell had occurred and that knockout mutant strains were produced. Antimicrobial tests were used to show the effects of deletion of *prcK* and *prcR* on the production of Paracin 1.7, and qRT-PCR was performed to determine whether the expression of *prcK* and *prcR* mRNA was affected. The data provided the basis for further exploration of the functions of these genes in the production of Paracin 1.7.

Materials and Methods

Bacterial strains, plasmids, growth medium and culture conditions

Bacterial strains and plasmids used in this work are listed in Table 1. *L. paracasei* HD1.7 strains were propagated in De Man-Rogosa-Sharpe (MRS) broth (Top Biotech Co., Qingdao, China) or agar at 30°C for 24 h. Where appropriate, tetracycline was added to the culture medium at 50 μg/mL. *E. coli* DH5α was grown in Luria-Bertani (LB) broth or agar at 37°C with vigorous agitation. *E. coli* DH5α transformant cells harbouring recombinant plasmids were selected onto LB agar plates supplemented with 100 μg/mL (final concentration) of ampicillin, 16 mL of X-Gal and 4 mL of IPTG per plate. *B.subtilis* ATCC 11774 was grown in Beef extract peptone (BP) broth or agar at 37°C, and this strain was used as an indicator strain when detect the antimicrobial activity.

DNA manipulation and transformation procedures

Genomic DNA isolation from *L. paracasei* HD1.7 was performed with TIANGEN genomic tips (Beijing, China). Plasmid isolation from *E. coli* DH5α transformants was done using TIANGEN plasmid Kit (Beijing, China). For amplication of DNA fragment was used procedure of PCR. The GE system[12] was used for the reaction system a PCR procedure. For screening purposes, DNA extractions from *L. paracasei* HD1.7 and *E. coli* DH5α colonies to be used as the template for PCR were carried out. PCR products were separated by 1% agar gel electrophoresis and were recovered using the Gel Extraction Kit (Tiangen Biotech CO., Beijing, China). The primers synthesis used in PCR reaction (Table 2) and PCR products sequencing were performed by Invitrogen Corporation.

Electroporation of *L. paracasei* HD1.7 was also carried out according to the method of Ge.[13] Transformation of *E. coli* DH5α competent cells were performed according to the Hannahan method.[14] Plasmids and restriction digestion products

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were analyzed by agar gel electrophoresis (120V, 20min).

Construction of *prcK, prcR* and *prcKprcR* knockout mutant of *L. paracasei* HD1.7, respectively

Restriction enzymes, T4 DNA ligase and DNA-modifying enzymes were used as recommended by the manufacturer (Tiangen, China). To delete the *prcK*, *prcR* and *prcKprcR* from the chromosome of *L. paracasei* HD1.7 by homologous recombination, plasmid pYTKLKRT, pYTRLRRT and pYTKRT were constructed (Figure 1).

The pYTKLKRT, a suicide plasmid, which was constructed by inserting a 1400 bp *Kpn*I fragment containing Tet^R, amplified from pMD18-T-tet using primers Tet-up and Tet-down, into the *Kpn*I site of pUC18-KLKR. Plasmid pUC18-KLKR was constructed by inserting a 1370 bp *Kpn*I/*Pst*I fragment containing *prcKR*, amplified from pMD18-T-KR using primers prcKR-up and prcKR-down, into the *Kpn*I and *Pst*I sites of plasmid pUC18-KL. Plasmid pUC18-KL was constructed by inserting a 1340 bp *Sac*I/*Kpn*I fragment containing *prcKL*, amplified from pMD18-T-KL using primers prcKL-up and prcKL-down, into the *Sac*I and *Kpn*I sites of pUC18.

Plasmid pYTRLRRT was constructed by inserting the 1400 bp *Kpn*I fragment containing Tet^R into the *Kpn*I site of pUC18-RLRR. Plasmid pUC18-RLRR was constructed by inserting a 1350 bp *Kpn*I and *Pst*I fragment containing *prcRR* (amplified from pMD18-T-RR by primers *prcRR*-up and *prcRR*-down) into the *Kpn*I and *Pst*I sites of plasmid pUC18-RL. Plasmid pUC18-RL was constructed by inserting a

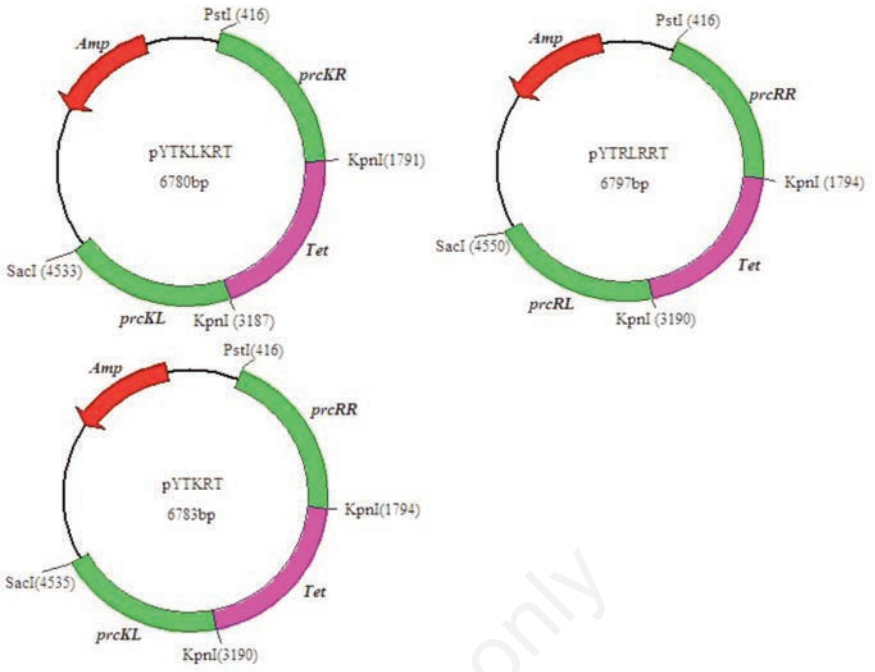

Figure 1. Structures of the pYTKLKRT, pYTRLRRT and pYTKRT plasmids.

Table 1. Strains and plasmids used in this study.

Bacterial strain or plasmid	Relevant features	Reference
L. paracasei HD1.7	Paracin 1.7 producer	Laboratory stock
E. coli DH5	Host strain for recombinant plasmids	Laboratory stock
B. subtlis ATCC 11774	Indicator strain for bacteriocin activity	Laboratory stock
pMD18-T	PCR cloning vector	Invitrogen
pYTKLKRT	*prcK* :: Tet^R suicide vector	This work
pYTRLRRT	*prcR* :: Tet^R suicide vector	This work
pYTKRT	*prcKprcR* :: Tet^R suicide vector	This work

Table 2. Primer sequences used in this study.

Primers	Primer sequences (5'→3')	Targets
prcK-up	ATGGAAACTTATTCTGATCTAGCCT	Amplify the whole *prcK* gene
prcK-down	AAGTCATCTCCCTATAAACAAAGTG	
prcKL-up	CCG*GAGCTC*(*Sac*I)TACCTTAATGATTTAGATGCGAGCG	Amplify the left homologous arm of *prcK* gene, used for construction of pYTKLKRT
prcKL-down	GTC*GGTACC*(*Kpn*I)GATTGTTCCTTCGGTGTGGATGTGT	
prcKR-up	GTC*GGTACC*(*Kpn*I)GGTTTTGCCGTCATCAGCGCACTTG	Amplify the right homologous arm of prcK gene, used for construction of pYTKLKRT
prcKR-down	CCG*CTGCAG*(*Pst*I)ACTAATCAGCTGGACTAAGGTGTAT	
prcRL-up	CCG*GAGCTC*(*Sac*I)CCTACTCAGCATTCAGAGGTCAACT	Amplify the left homologous arm of *prcR* gene, used for construction of pYTRLRRT
prcRL-down	GTC*GGTACC*(*Kpn*I)ATCTTCAGCATCGTTTGGTGGTTGG	
prcRR-up	GTC*GGTACC*(*Kpn*I)GGTCAGCATTCGTAGAGTGTCGGCC	Amplify the right homologous arm of *prcR* gene, used for construction of pYTRLRRT
prcRR-down	CCG*CTGCAG*(*Pst*I)GCAGTGACCAGAGATAGCTCGGCGT	
Amp-up	CTT*AGATCT* (*Bgl* II)ACCAATGCTTAATCAGTGAGG	Amplify the ampicillin resistance gene used in pUC18
Amp-down	CGG*AGATCT* (*Bgl* II)GGAACCCCTATTTGTTTATTT	
Tet-up	CCG*GGTACC* (*Kpn* I)TCTCATGTTTGACAGCTT	Amplify the tetracycline resistance gene used in pBR322
Tet-down	GTC*GGTACC* (*Kpn* I)TAATAGATATGTTCTGCCAAGGGT	
prcR-up	ATGACNAAYCAYCARAC	Verify the suicide plasmids pYTRT
prcR-down	TGCCAGGTTATGGGAAT	
ldh-up	GACACATAAGAAAGGATG	Amplify the whole *ldh* gene
ldh-down	TACTGACGAGTTTCGATGTC	

1350 bp *Sac*I/*Kpn*I fragment containing *prcRL*, amplified from pMD18-T-RL using primers *prcRL*-up and *prcRL*-down, into the *Sac*I and *Kpn*I sites of plasmid pUC18.

Plasmid pYTKRT was constructed by inserting the 1400 bp *Kpn*I fragment containing Tet^R into the *Kpn*I site of pUC18-KLRR. Plasmid pUC18-KLRR was constructed by inserting a 1370 bp *Kpn*I/*Pst*I fragment containing *prcRR*, amplified from pMD18-T-RR, into the *Kpn*I and *Pst*I sites of plasmid pUC18-KL.

Three recombinant plasmids were transformed by electroporation into *L. paracasei* HD1.7 cells. The *prcK* and *prcR* mutant strains were selected by plating out appropriate dilutions on MRS agar containing 50 µg/mL (final concentration) of tetracycline. Restriction enzyme analysis and PCR identification were used to investigate whether the suicide plasmids met the experimental design.

Bacteriocin production of the original and the mutant strains

To evaluate bacteriocin production, the cultures of the parental and the mutant strains were inoculated into MRS broth and incubated at 37°C for 24 h, respectively. The supernatants from cultures were collected for determination of bacteriocin activity using the agar-well diffusion method described by Nwuche.[15] To eliminate the antimicrobial effect of lactic acid, the pH of the supernatants were adjusted to 5.5 with 1 M NaOH. Titers were defined as the reciprocal of the highest dilution that inhibited the growth of the indicator strain. The results of the bacteriocin activity assays are presented in arbitrary units per milliliter (AU/mL).

RNA isolation, cDNA synthesis and qRT-PCR

The cultures of the parental and the mutant strains were inoculated into MRS broth and incubated at 37°C for 12 h, respectively. Both these cultures were harvested to extract and purify their RNA. Isolation total RNA was carried out with RNAprep Pure Cell/Bacteria Kit (Tiangen, China) in accordance with the manufacturer's recommendations. RNA concentration was measured at 260 nm and RNA purity was determined by measuring the absorbance ration at 260 nm/280 nm with A560 spectrophotometer (AOE INSTRUMENTS, Shanghai, China).

Reverse transcription was completed using BioRT cDNA First Strand Synthesis Kit (Bioer Technology, China) as instructed. Controls without reverse transcriptase were included in the qRT-PCR runs in order to confirm absence of contaminating DNA.

qRT-PCR amplications were performed with at least 3 replicates using RealMasterMix SYBR Green reagents (Tiangen, China) in a 7500 Real-Time PCR System (Applied Biosystems, Inc., USA). The housekeeping gene *ldh* was used as internal control *L. paracasei* HD1.7. The suitability of *ldh* was verified by isolation of both genomic DNA and RNA during the experiments. Transcriptional levels of *prcK* and *prcR* were normalized to the transcriptional level of the *ldh* gene.

Results

Antimicrobial activity of knockout mutant strains

Three single colonies growing well on the MRS resistant plates with tetracycline were selected as *prcK* knockout mutant strain (ΔK), *prcR* knockout mutant strain (ΔR), and *prcKprcR* knockout strain (ΔKR).

The antimicrobial activity of ΔK, ΔR and ΔKR were shown in Figure 2. The results showed that the inhibition degrees of ΔK, ΔR and ΔKR were 23.61% (1538.29±46.27 AU/mL), 21.93% (1572.26±39.04 AU/mL), and 36.61% (1276.53±21.26 AU/mL) lower than that of original strain (2013.80±26.54 AU/ml), respectively, this indicated that the outputs of bacteriocin produced by three mutant strains were less than that of original strain, and the output of ΔKR was obviously less than those of ΔK and ΔR.

However, ΔK and ΔR still had inhibition ability to the growth of *B. subtilis*. That was probably due to *L. paracasei* HD1.7 having several quorum sensing systems. Other systems would not be impacted if one system was disrupted. Therefore, the mutants still could produce some antimicrobial peptides. Furthermore, the inhibition degree of ΔKR was 36.6% lower than that of the wild-type strain, obviously a greater effect than in ΔK or ΔR. Knocking out one gene would negatively influence the regulation of the quorum sensing system and lead to a decrease in production of antimicrobial peptides. Knocking out two genes in ΔKR apparently further increased the negative influence on the regulation of quorum sensing system, leading to a lower production of antimicrobial peptides in ΔKR than in ΔK or ΔR.

PCR analysis of *prcK* and *prcR* knockout mutant strains

Amplification of both Tet^R and (*prcK* + Tet^R) by PCR was used to identify whether homologous recombination between suicide plasmids and genome of host cells had accomplished, which was based on the theoretical design.

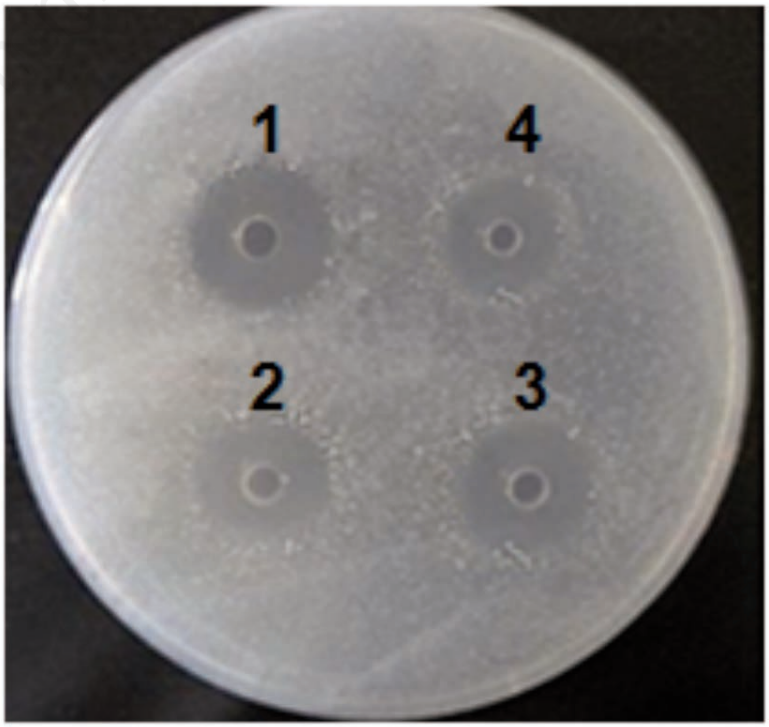

Figure 2. Antibacterial efficacy of mutant and parental *L. paracasei* HD1.7 strains against *B. subtilis*. 1, 2, 3 and 4 represent the inhibition zones of parental strains, △K, △R and △KR , respectively (pH 5.5).

For PCR analysis of ΔK, genomic DNA of ΔK and the primers Tet-up and Tet-down were used as template and the primers, respectively. The original strain *L. paracasei* HD1.7 was used in the negative control experiment. It was the same with ΔR and ΔKR. The results of agarose gel electrophoresis were shown in Figure 3. There was a 1400 bp DNA fragment (Tet^R) that was amplified in ΔK, ΔR, and ΔKR, but no similar fragment in the negative control experiment, which demonstrated that Tet^R was inserted into the genomes of ΔK, ΔR, and ΔKR.

For PCR identification of ΔK, genomic DNA of ΔK and the primers *prcKL*-up and *prcKR*-down were used as template and the primers, respectively. The original strain *L. paracasei* HD1.7 was used in the negative control experiment. ΔR (primers *prcRL*-up and *prcRR*-down) and ΔKR (primers *prcKL*-up and *prcRR*-down) were also identified as described above.

The results of agarose gel electrophoresis were shown in Figure 4. The results of Figure 4A showed that there was a 4140 bp DNA fragment (*prcK* + Tet^R) that were amplified in ΔK and a 2740 bp fragment (only *prcK*) in the negative control experiment. The results of Figure 4B showed that there was a 4820 bp DNA fragment (*prcR* + Tet^R) that was amplified in ΔR and a 3420 bp fragment (only *prcR*) in the negative control experiment. The results of Figure 4C showed that there was a 4130 bp DNA fragment (*prcKL* + *prcRR* + Tet^R) that was amplified in ΔKR and a 3500 bp fragment (only *prcK*+*prcR*) in the negative control experiment. It was demonstrated that Tet^R was successfully inserted into *prcK, prcR and prcKprcR*, respectively. Therefore, double cross-over occurred in ΔK, ΔR and ΔKR. The *prcK*, *prcR* and *prcKprcR* knockout mutant strains were constructed successfully.

qRT-PCR analysis of *prcK* and *prcR* knockout mutant strains

Relative transcriptional expression of *prcK* and *prcR* in the parental and the mutant *L. paracasei* HD1.7 are present in Figure 5. There were significant reductions ($p < 0.01$) in *prcK* and *prcR* transcriptional levels in the parental and the mutant *L. paracasei* HD1.7. The level of *prcK* mRNA in ΔK was 0.36:1 compared with the parental strain. For ΔR, the corresponding ratio was 0.33:1. These results indicate that the bacteriocin produced by the mutant *L. paracasei* HD1.7 was indeed mediated by the action of *prcK* and *prcR* genes. As a consequence, the results of qRT-PCR analysis are consistent with the analysis of PCR and antimicrobial activity.

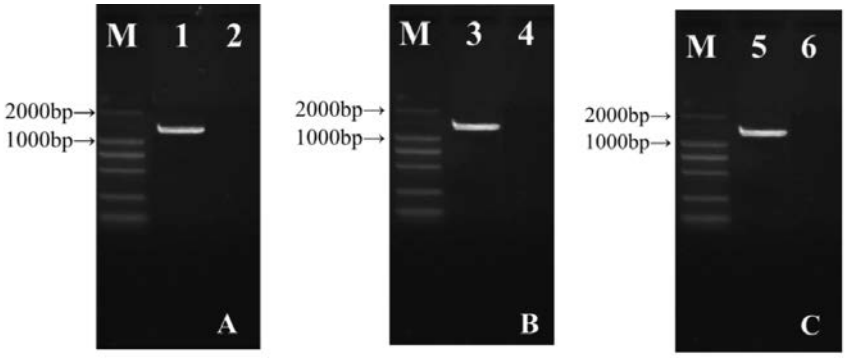

Figure 3. PCR screening results using different templates with Tet-up and Tet-down primers. M: DNA Marker DL 2000; Lane 1, 3, 5: the PCR product using △K, △R and △KR gDNA as template, respectively; Lane 2, 4, 6: the PCR product using the original strain gDNA as template.

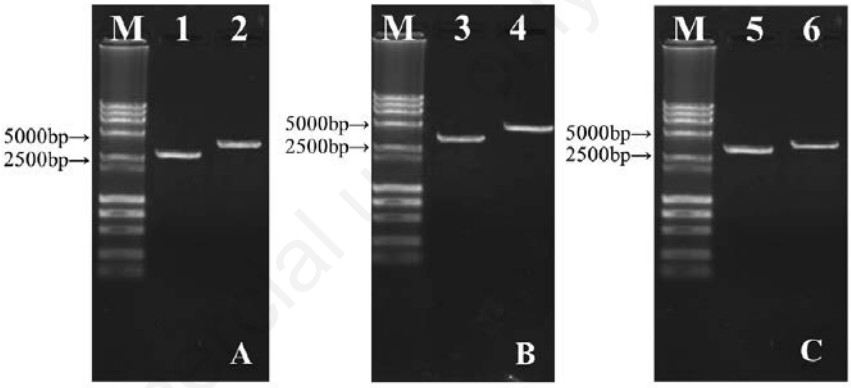

Figure 4. PCR screening for gene knockouts using various primer pairs. (A) The PCR identification result with prcKL-up and prcKR-down primers. (B) The PCR identification result with prcRL-up and prcRR-down primers. (C) The PCR identification result with prcKL-up and prcRR-down primers. M: DNA Marker DL 15000 + 2000; Lane 1, 3, 5: the PCR product using the original strain gDNA as template; Lane 2, 4, 6: the PCR product using △K, △R and △KR gDNA as template, respectively.

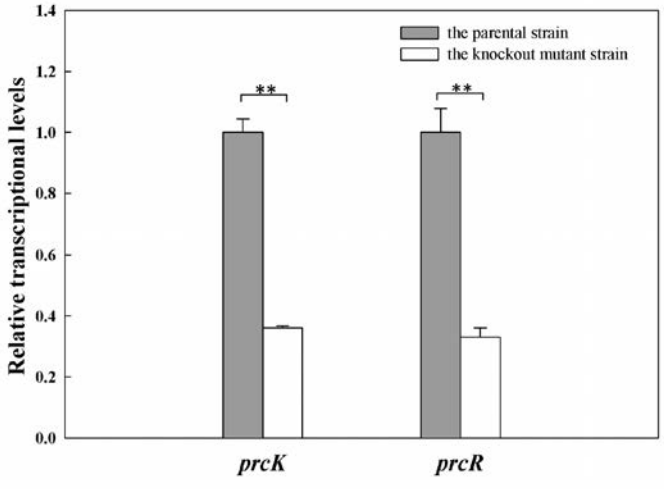

Figure 5. Relative transcriptional expression of prcK and prcR in the parental (■) and the mutant (□) L. paracasei HD1.7. Asterisk indicates a statistically significant difference ($p < 0.01$) with respect to the control group.

Discussion and Conclusions

Quorum sensing of Gram-positive bacteria is often regulated by three-component regulatory system composed of autoinducing peptide, sensor kinase and response regulator.[16] When the extracellular AIPs concentration reaches the threshold, specific receptor enzyme proteins can be activated and bind to the histidine protein kinase (HPK) receptors on the cell membrane. The HPK autophosphorylates its own histidine residue and then transfers the phosphate group to the asparitic acid in a response regulator (RR). It has been confirmed that the process of producing bacteriocin from a variety of lactic acid bacteria is regulated by the QS system, such as *L. sanfranciscensis*,[17] *L. acidophilus*[18,19] and *L. plantarum*.[20,21]

A series of genes mediated quorum sensing and production of Paracin1.7 by *L. paracasei* HD1.7 has been reported before. Previously, We have demonstrated that the process of producing bacteriocin of *L. paracasei* HD1.7 is regulated by quorum sensing via the cell density test.[13] Here, we showed that the inhibition ability of *L. paracasei* HD1.7 decreased after knocking out the *prcK* and *prcR* genes. This finding suggests that *prcK* and *prcR* are quorum sensing related genes and influence the production of antimicrobial peptides as *plnB* has been observed for *L. paraplantarum* L-XM1.[22]

Different studies have shown the role of *prcK* and *prcR* in the quorum sensing system. In the study of Nakayama,[2] the fragment of *L. paracasei* E93490 amplified by degenerate primers was located in the *prcK* gene prior to *prcR*. Their predictive products PrcK and PrcR are similar to cognate HPK and RR, respectively, and the highest sequence similarity was *L. sake* SppK and *L. plantarum* PlnB, both of which formed a 3CRS that regulates the formation of bacteriocin. PrcK is expected to have six transmembrane alpha-helices at its N-terminal moiety, which can be used as a sensor domain. Similarly, the effect of *prcK* and *prcR* of *L. paracasei* HD1.7 on regulation of bacteriocin production needs further investigation.

In conclusion, the present study shows that the *prcK* and *prcR* genes of *L. paracasei* HD1.7 were down-regulated in response to the inhibition ability of ΔK and ΔR. These findings suggested that *prcK* and *prcR* are quorum sensing related genes and influence the production of antimicrobial peptides. This provides the basis for further exploration of the productions of natural preservatives.

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