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MINI-REVIEW

Mechanisms and improvement of acid resistance in lactic acid bacteria

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Abstract Lactic acid bacteria (LAB) can take advantage of fermentable carbohydrates to produce lactic acid. They are proverbially applied in industry, agricultural production, animal husbandry, food enterprise, pharmaceutical engineering and some other important fields, which are closely related to human life. For performing the probiotic functions, LAB have to face the low pH environment of the gastrointestinal tract. Therefore, acid resistance of LAB is of great importance not only for their own growth, but also for fermentation and preparation of probiotic products. Recent research studies on acid resistance mechanisms of LAB are mainly focused on neutralization process, biofilm and cell density, proton pump, protection of macromolecules, pre-adaptation and cross-protection, and effect of solutes. In this context, biotechnological strategies such as synthetic biology, genome shuffling, high pressure homogenization and adaptive laboratory evolution were also used to improve the acid resistance of LAB to respond to constantly changing low pH environment.

Keywords Lactic acid bacteria · Acid stress · Acid resistance mechanism · Biotechnology

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Introduction

Lactic acid bacteria (LAB) belong to a large category of Gram-positive bacteria that can be found in daily environments as well as in the human gastrointestinal tract (GIT) (Gaspar et al. 2013). Besides, some LAB are economic fermentative bacteria with probiotic properties in GIT (Wu et al. 2009; Koponen et al. 2012; Zhai et al. 2014).

LAB are usually faced with stable low pH or sudden and transient acid stress (Koponen et al. 2012; Wu et al. 2009; Broadbent et al. 2010). During their growth, cellular machinery excretes lactic acid that can be imported back. It lowers the cytoplasmic pH, which can inhibit the growth of cells and may even lead to death (Koponen et al. 2012; Wu et al. 2012a). Several mechanisms are involved in the acid resistance regulation of LAB, including central metabolic pathways, proton pump, changes of cell membrane composition and cell density, DNA and protein damage repair, as well as neutralization processes (Cotter and Hill 2003; Koponen et al. 2012; Wu et al. 2014; Liu et al. 2015).

This article discusses the mechanisms used by LAB for adaptation in low pH environment, and techniques of biotechnology, which have been utilized to enhance the acid resistance of LAB.

Mechanisms of acid resistance

Neutralization processes

Arginine dihydrolase system (ADS)

Microorganisms produce alkaline substances such as urea, arginine and ammonia, which neutralize the acids. Urease hydrolyzes urea into carbon dioxide and ammonia. Arginine

dihydrolase also called arginine deiminase is the part of the pathway, named after them as arginine dihydrolase system (ADS) which catalyzes the conversion of arginine into ornithine, ammonia and carbon dioxide.

Generally, ADS contains three enzymes in LAB, including arginine dihydrolase (EC 3.5.3.6), ornithine transcarbamylase (EC 2.1.3.3), and carbamate kinase (EC 2.7.2.2). They are encoded by an operon, *arcABC* (Maghnouj et al. 1998; Arena et al. 1999, 2002; Champomier et al. 1999). Compared with the wild-type strain *Lactobacillus casei* Zhang, its acid-resistant mutant displayed higher intracellular aspartate and arginine levels in the acidic environment (Wu et al. 2013a). During acid stress, aspartate enhances the flux of metabolites towards arginine biosynthesis. The acid resistance ability of *L. casei* was enhanced by the addition of 50 mM arginine or aspartate (Wu et al. 2012a). It indicated that arginine and aspartate are related to acid resistance regulation of strains (Wu et al. 2012a, 2013a; Zhang et al. 2012).

Furthermore, agmatine deiminase system and tyrosine catabolic pathway, which are encoded by the same locus in the chromosome, are beneficial to acid resistance of *Lactobacillus brevis* (Lucas et al. 2007). It was speculated that ammonia was formed from agmatine through the agmatine deiminase system to neutralize protons in cells to maintain intracellular pH homoeostasis in *L. brevis*, when encountered with low pH environment (Lucas et al. 2007).

Malolactic fermentation

Another promising acid resistance mechanism is malolactic fermentation (Solieri et al. 2010; Broadbent et al. 2010). Malolactic fermentation (MLF) carried out by a variety of LAB, including *Oenococcus oeni*, and the members of the genera of *Lactobacillus*, and *Leuconostoc* etc (Solieri et al. 2010; Broadbent et al. 2010; Bravo-Ferrada et al. 2013). MLF is a decarboxylation of L-malate to yield L-lactic acid. Carbon dioxide is liberated in the process which neutralizes the protons and decreases their concentration (Sumby et al. 2014). MLF improved the survival ability of *L. casei* ATCC 334 in low pH environment. Reportedly, addition of 30 mM malate can enhance the acid resistance of the strain at pH 2.5 (Broadbent et al. 2010).

Biofilm and cell density

Generally, a group of microorganisms with a protective slimy sheath which is made up of DNA, proteins, and polysaccharides, constitute biofilm. It is the first barrier of the cell and has the ability to withstand environmental disruption. Modifying physicochemical properties of biofilm has proved to be an important survival strategy for many microorganisms (Hall-Stoodley and Stoodley 2009). When faced with low pH environment, there is a rise of membrane mobility and ratio of unsaturated fatty acids, and their mean chain length indicating that changing fluidity of biofilm, distribution of fatty acids, and integrity of cells may be potential methods for LAB to enhance acid resistance (Wu et al. 2012b). Studies have shown that ratio of cyclopropane fatty acids (CFA) remarkably changed in strains under low pH environment, indicating that CFA has a potential role in strains to cope with acidic environment (Broadbent et al. 2010; Wu et al. 2012b).

On the contrary, cyclopropanation of unsaturated fatty acid is found non-essential for acid resistance of *Lactobacillus lactis* subsp. *cremoris* and solely CFA could not preserve mobility level of biofilm (To et al. 2011). Hence, it is necessary to further investigate the specific protective effects of CFA under acid stress.

Biofilm formation is not only affected by changing pH, osmotic pressure, carbohydrate concentration in the environment, but also regulated by signaling molecules (Costerton et al. 1995). In *Lactobacillus bulgaricus*, central metabolic network genes bring about rerouting of pyruvate metabolism to induce modifications of fatty acid composition, and then influence mobility of biofilm, which will help them to overcome various low pH conditions (Fernandez et al. 2008).

Proton pump

F_1-F_0-ATPase

F_1-F_0-ATPase can hydrolyze or synthesize intracellular ATP through F1 protein, and transport proton through F_0 complex. It is a substantial component of acid tolerance, and its activity is positively related with the more acid resistance in LAB (Kajfasz and Jr 2011). The F_1-F_0-ATPases of some LAB have been well identified, including *Lactococcus lactis, Lactobacillus helveticus, Lactobacillus acidophilus, Lactobacillus rhamnosus*, and *O. oeni* etc (Yokota et al. 1995; Yamamoto et al. 1996; Tourdot-Marechal et al. 1999; Kullen and Klaenhammer 1999; Koponen et al. 2012). Transcriptional levels of *atp* which encodes F_1-F_0-ATPase in *L. acidophilus* were found high when encountered with low pH environment (Kullen and Klaenhammer 1999). Similarly, low pH induced the expression of F_1-F_0-ATPase genes in *L. rhamnosus* GG (Koponen et al. 2012). The mutations of F_1-F_0-ATPases lead to lower survival of LAB at low pH (Yokota et al. 1995; Yamamoto et al. 1996; Tourdot-Marechal et al. 1999). The acid-resistant derivative strain *L. casei* Lbz-2 displayed greater H^+-ATPase activity than its wild-type *L. casei* Zhang (Wu et al. 2012a). At the same time, it showed a higher intracellular pH than *L. casei* Zhang at low pH (Wu et al. 2012a).

Amino acid decarboxylation

Another mechanism associated with proton depletion is the amino acid decarboxylation-antiporter reaction (Azcarate-Peril et al. 2004). It can maintain intracellular pH homoeostasis in a decarboxylation reaction by consuming protons. For example, glutamate decarboxylase (GAD) can catalyze the conversion of glutamate to γ-aminobutyrate (GABA), and results in the raising of the intracellular pH (Feehily and Karatzas 2013). The expression of genes encoding GAD in *L. acidophilus* is strongly increased in gastric juice (Wilson et al. 2014). Four putative genes involved with decarboxylation reactions from *L. acidophilus* NCFM were disrupted by means of insertional inactivation, including an ornithine decarboxylase, an amino acid permease, a glutamate-aminobutyrate antiporter, and a transcriptional regulator (Azcarate-Peril et al. 2004). All mutants were more sensitive to low pH than the parental strain. The results indicated that the decarboxylation reaction played an important role in the improvement of acid resistance of strains. On the same note acid resistance of *L. lactis* was enhanced by heterologous expression of histidine decarboxylation pathway with the aid of histidine in acidic environment (Trip et al. 2012).

Protection and repair of cellular macromolecules

Low pH environment brings a selection pressure on LAB for survival fitness. As cytoplasmic pH decreases, the mechanisms to protect the major biological molecules such as DNA and proteins kick in Wu et al. (2012a).

The *uvrA* gene codes for subunit A of the ultraviolet excinuclease ABC complex, which involves in the nucleotide excision repair mechanism. Its transcriptional activity was activated by exposure to ultraviolet radiation. The expression of *uvrA* was significantly induced during acid-adaptation in *L. helveticus* (Cappa et al. 2005). Similarly, a moderate ultraviolet irradiation improved an acid tolerance in *Lactococcus lactis* subsp. *lactis* (Hartke et al. 1995). One can conclude that UvrA and nucleotide excision repair pathways have vital functions in the repair process of DNA damage caused by acid and are guarantees for the strains to favorably adapt to the acidic environment (Hartke et al. 1995; Cappa et al. 2005).

Although their precise role in acid adaptation of LAB is not fully understood, some general stress proteins were detected as more abundant in acid-stressed LAB, such as chaperones (DnaK, GrpE, GroEL, and GroES), and small heat shock proteins (Hsp1, Hsp3, and Shsp) etc (De Angelis and Gobbetti 2004; Fernandez et al. 2008; Lee et al. 2008; Wu et al. 2009, 2011, 2012a; Heunis et al. 2014). It is suggested that the molecular chaperones like DnaK can enhance biosynthesis of F_1-F_0-ATPase, which help the cell to remove protons to maintain intracellular pH homoeostasis (Kim and Batt 1993; Walker et al. 1999). For example, *dnaK* from *E. coli* was introduced into *L. lactis* NZ9000, and it enhanced acid resistance of strain in acidic environment (Abdullah et al. 2010). Heterogeneous expression of a small heat shock protein, Shsp, encoded by *shsp* from *Streptococcus thermophilus* in *L. lactis* ML23 had resulted in higher survival under acid stress (Tian et al. 2012). DNA repair protein RecO, encoded by *recO* in *L. casei*, once expressed in *L. lactis* NZ9000 increased acid resistance of strain under acidic conditions (Wu et al. 2012a, 2013b).

Likewise, accumulation of trehalose and glutathione protects the cellular proteins from acid stress. For example, the trehalose accumulation is response to acid stress in *Propionibacterium freudenreichii* (Cardoso et al. 2004). In order to study the potential effects of trehalose, its de novo biosynthetic pathway of *P. freudenreichii* was introduced into *L. lactis*, as expected, the recombinant strain exhibited higher acid resistance than the control strain (Carvalho et al. 2011). *gshA* and *gshB* are related to glutathione biosynthesis in *E. coli*. Their heterologous expression in *L. lactis* NZ9000, enhanced the acid resistance of the strain indicating the relationship between glutathione and acid resistance of strains (Zhang et al. 2007). Reportedly, addition of 3–6 mM glutathione can protect LAB from low pH (Kim et al. 2012).

Pre-adaptation and cross-protection

Pre-adaptation is the process of treating a strain to lethal or sub-lethal doses of the stress for a limited time, which accentuates the recovery of the strain when exposed to the natural stress. The mechanism behind pre-adaptation is not well understood. *L. casei* ATCC 334 was pre-treated for 20 min at a pH value of 4.5, which enhanced the resistance of the strain for low pH (Broadbent et al. 2010). Cross-protection works on the principle that interrelated responses are generated by different stress conditions. In other words, different stimuli like heat, oxygen, cold and low pH may generate similar responses. For example, heat pre-treatment induced an acid resistance response (ATR) in *Lactobacillus plantarum* which promoted its growth under low pH (De Angelis et al. 2004). Wang et al. obtained high acid tolerance strains by ultraviolet irradiation and heat pre-treatments (Wang et al. 2007). In summary, pre-adaptation and cross-protection are effective methods to strengthen the resistance of LAB against acidic environments. However, exact molecular mechanisms need further research.

Use of protective substances

Addition of protective substances is a comparatively simple and direct method to reduce the damage caused by acidic environment. Many kinds of protective agents are used to resist damage caused by acidic environment in LAB, most of

which include amino acids, fatty acids, and sugars. Addition of arginine and aspartate can improve acid resistance of *L. casei* Zhang under acidic environment (Zhang et al. 2012; Wu et al. 2013a). When Tween-80 was added to the culture of *L. rhamnosus*, the strain showed 1000-fold higher survival fitness than control (Corcoran et al. 2007). Addition of glutathione also protected LAB from low pH (Kim et al. 2012).

Use of high-throughput techniques for acid resistance in LAB

In recent years, a lot of genomics studies of LAB are completed and published. For example, largest and most diverse genus, *Lactobacillus* in LAB, contains about 214 genome sequencing projects in public databases (Stefanovic et al. 2017). The genomic studies of LAB have helped to understand their metabolic processes. The same information has been utilized for their application in industry (Zhu et al. 2009; Stefanovic et al. 2017). The advent of genomics provides a possibility to modify the strain for purposeful exploitation on the basis of a more knowledge-based approach (Stefanovic et al. 2017).

Synthetic biology is an interdisciplinary science, which combines many disciplines like genetic engineering, systems biology, biophysics, computer engineering and evolutionary biology (Zhu et al. 2012). Synthetic biology is widely applied in medical and food industries by means of building artificial biological systems. Concurrently, it accelerates our understanding of mechanisms of biology. It offers a new approach for improvement of the acid tolerance of LAB. For example, *Bacillus coagulans* SIM-7 DSM 14043 is a novel lactic acid producing strain with high acid tolerance (Michelson et al. 2006). Acid-resistant components of *B. coagulans* SIM-7 DSM 14043 can be sythesized through synthetic biology and transformed into other LAB. Synthetic biology has a great potential to enhance the acid resistance in LAB.

Genome shuffling is an efficient method for the rapid improvement of important microbial phenotypes. It consists of four steps, which are (i) construction of a mutant library by classical strain-improvement methods, (ii) screening of number of positive mutants, (iii) undertaking multiple rounds of protoplast fusion to generate many random mutants and (iv) screening of strains for the expected phenotypes (Stephanopoulos 2002). Obtaining multitrait phenotypes by means of traditional methods is difficult but genome shuffling can engineer such strains in less time (Stephanopoulos 2002). This approach has been used to improve acid tolerance in LAB (Patnaik et al. 2002; Wang et al. 2007; Triratna et al. 2011). New shuffled LAB can grow at substantially lower pH than does the wild-type strain (Patnaik et al. 2002; Wang et al. 2007; Triratna et al. 2011).

In food industry, some non-thermal pasteurization processes have been utilized. These methods like pulsed electric field (PEF) and high pressure homogenization (HPH) do not use heat; therefore, sensorial and nutritional properties of food products are not affected. Amazingly, these processes can improve functional properties of strains (Cueva 2009; Muramalla and Aryana 2011; Tabanelli et al. 2013).

PEF involves the application of pulses of high voltage (20–80 kV/cm) to fluid placed between two electrodes for less than one second (Cueva 2009). The effect of PEF treatment on acid tolerance of *L. acidophilus* LA-K was evaluated and the results indicated that specific PEF conditions can improve the acid tolerance of the strain (Cueva 2009). In HPH process, the samples in a liquid are homogenized in a range of different pressures. Generally, it is considered that HPH has a close relationship with improvement of sensorial or functional properties of fermented milks and cheeses (Patrignani et al. 2009). In recent years, HPH is used in modification of the functional properties of LAB like acid tolerance and bile tolerance (Muramalla and Aryana 2011). Acid tolerance of *L. acidophilus* LA-K had been enhanced using HPH at 13.8 MPa (Muramalla and Aryana 2011). The same effects were observed for *L. delbrueckii* ssp. *bulgaricus* LB-12 and *S. salivarius* ssp. *thermophilus* ST-M5 (Muramalla and Aryana 2011). Similarly, sub-lethal HPH-treated *L. paracasei* A13 exhibited higher acid resistance compared with controls (Tabanelli et al. 2013). These results indicate that PEF and HPH can be recommended for increasing probiotic characteristics of LAB, including acid tolerance.

Adaptive laboratory evolution (ALE) is a method that explores the natural adaptation of microorganisms over time to the artificial selection pressures given in the laboratory. The different techniques employed in ALE are DNA sequencing, high-throughput screening and gene manipulation (Portnoy et al. 2011). This approach is used in improvement of the acid tolerance of *L. casei* Zhang (Zhang et al. 2012). The evolved mutant lb-2 was obtained in 70 days with serially exposing exponentially growing strains to low pH conditions. The strain showed a 318-fold higher survival rate than the parental strain at pH 3.3 for 3 h (Zhang et al. 2012).

Conclusion

Lactic acid bacteria are always encountered with acidic environment and they have developed various mechanisms to improve their acid resistance (Fig. 1). Emergence of high-throughput techniques brings the improvement in acid resistance of LAB. LAB with high acid resistance had been generated by these approaches. It is important to fully understand the mechanisms of acid resistance in LAB as it will accentuate the benefits of probiotics for humankind.

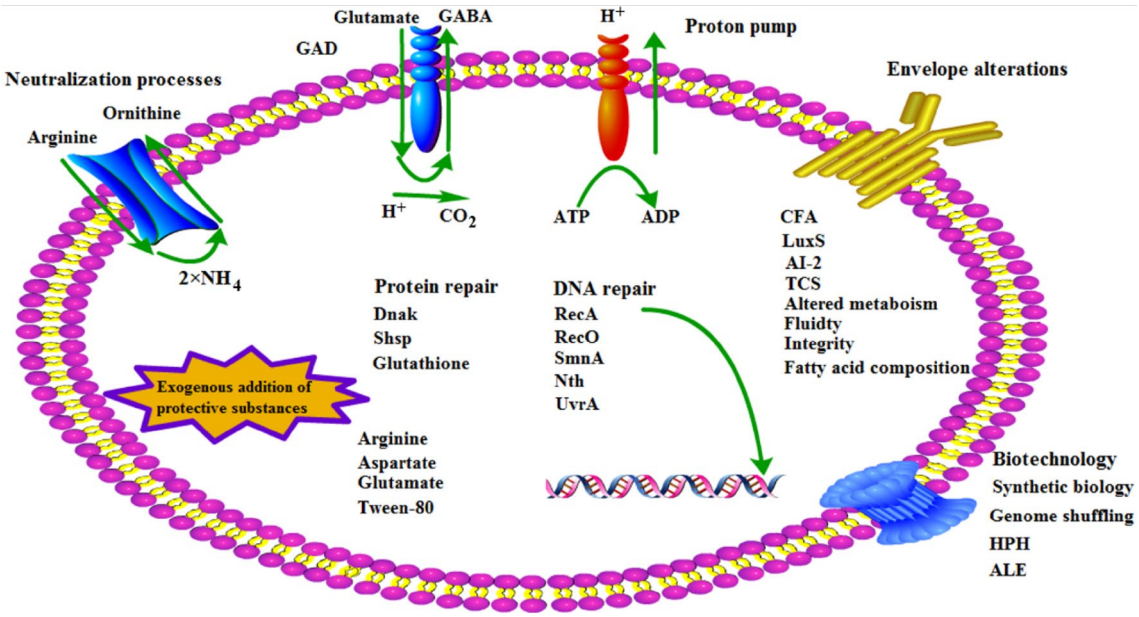

Fig. 1 Mechanisms of acid tolerance in LAB. *ADP* adenosine diphosphate, *AI-2* auto-inducer 2, *ALE* adaptive laboratory evolution, *ATP* adenosine triphosphate, *CFA* cyclopropane fatty acids, *Dnak* molecular chaperone protein, *GABA* γ-aminobutyrate, *GAD* glutamate decarboxylase, *HPH* high pressure homogenization, *LuxS* S-ribosylhomocysteinelyase, *Nth* endonuclease, *RecA* DNA repair protein, *RecO* DNA repair protein, *Shsp* small heat shock protein, *SmnA* AP endonuclease, *TCS* two-component signal system, *UvrA* ultraviolet excinuclease

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

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