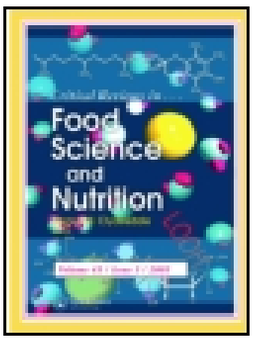

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REVIEW

Recent advances in understanding the effect of acid-adaptation on the cross-protection to food-related stress of common foodborne pathogens

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ABSTRACT

Acid stress is one of the most common stresses that foodborne pathogens encounter. It could occur naturally in foods as a by-product of anaerobic respiration (fermentation), or with the addition of acids. However, foodborne pathogens have managed to survive to acid conditions and consequently develop cross-protection to subsequent stresses, challenging the efficacy of hurdle technologies. Here, we cover the studies describing the cross-protection response following acid-adaptation, and the possible molecular mechanisms for cross-protection. The current and future prospective of this research topic with the knowledge gaps in the literature are also discussed. Exposure to acid conditions (pH 3.5 – 5.5) could induce cross-protection for foodborne pathogens against subsequent stress or multiple stresses such as heat, cold, osmosis, antibiotic, disinfectant, and non-thermal technology. So far, the known molecular mechanisms that might be involved in cross-protection include sigma factors, glutamate decarboxylase (GAD) system, protection or repair of molecules, and alteration of cell membrane. Cross-protection could pose a serious threat to food safety, as many hurdle technologies are believed to be effective in controlling foodborne pathogens. Thus, the exact mechanisms underlying cross-protection in a diversity of bacterial species, stress conditions, and food matrixes should be further studied to reduce potential food safety risks.

HIGHLIGHTS

- Foodborne pathogens have managed to survive to acid stress, which may provide protection to subsequent stresses, known as cross-protection.
- Acid-stress may induce cross-protection to many stresses such as heat, cold, osmotic, antibiotic, disinfectant, and non-thermal technology stress.
- At the molecular level, foodborne pathogens use different cross-protection mechanisms, which may correlate with each other.

KEYWORDS

Fermentation; food safety; molecular mechanisms; multiple stresses; non-thermal processing; thermal processing

Introduction

Foodborne pathogens survive many stresses at all stages of the food chain, starting from production, then harvest/post-harvest, food processing, and finally all the way through the digestive tract of the human host (Hu et al. 2020). The concentration of protons (H^+), measured as pH, and the acid type are conditions that have a great impact on growth and survival of foodborne pathogens. Challenges arise for microorganisms when the pH is low, which can occur through natural geochemical processes, microbial metabolic processes that generate organic acid by-products, or the addition of organic acids to the food (Lund et al. 2020). Sophisticated mechanisms at the physiological and molecular levels have been developed by foodborne pathogens to survive and adapt to acid stress (Guan and Liu 2020). Pathogens typically respond to acid stress by preventing a damaging drop in intracellular pH below a threshold level necessary for viability (Lund et al. 2020). Just like antibiotic-resistant bacteria, the emergence of acid-resistant foodborne pathogens could bring great pressure to the food industry during processing and storage. Acid-resistant bacteria may pass through the human gastrointestinal tract, posing a real threat to human health (Lee and Kim 2017). There are several mechanisms underlying the acid-adaptation response in foodborne pathogens including the maintenance of pH homeostasis, cell membrane integrity and fluidity, metabolic regulation, and macromolecule repair (Guan and Liu 2020).

Acid-adaptation response, in addition to conferring resistance to low pH, may also induce a series of physiological and genetic resistance mechanisms conferring advantages to the bacteria to resist to another stress. These phenomena are called cross-protection responses (Wang, Buchanan, and Tikekar 2019). In addition to low pH achieved by fermentation or addition of organic acids, most

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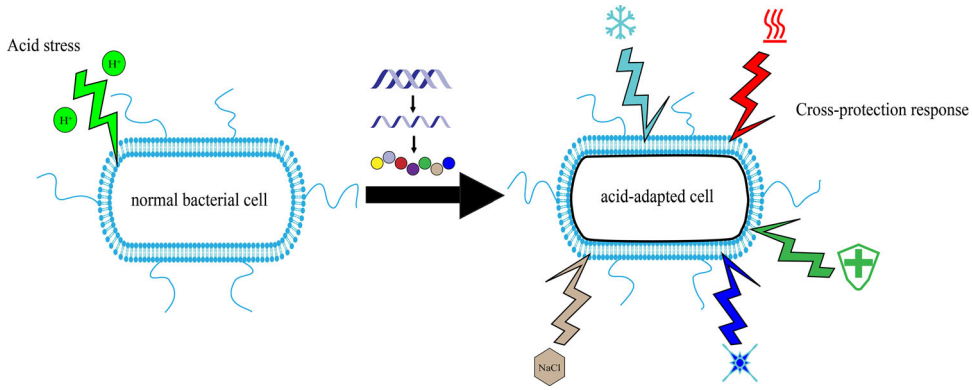

Figure 1. Overview of cross-protection response induced by acid-adaptation in foodborne pathogens.

foods at industrial scale pass through a series of processes such as cooking, heating, marination, and refrigeration (Liao et al. 2020). Thus, foodborne pathogens may encounter a variety of stresses in the environment as a result of food processing (Wang, Buchanan, and Tikekar 2019). Furthermore, there is evidence that the acid tolerance response can induce cross-protection in foodborne pathogens against subsequent stresses during processing such as heat, cold, osmotic stress, antibiotics, ultraviolet (UV) irradiation, or high hydrostatic pressure, representing a potential risk to food safety (Lund et al. 2020; Bonnet and Montville 2005; Haberbeck et al. 2017; Greenacre and Brocklehurst 2006; Wang, Buchanan, and Tikekar 2019).

Considering that most foodborne pathogens encounter acid conditions and subsequent food-related stress throughout the food chain, it is imperative to provide detailed descriptions of the cross-protection responses of foodborne pathogens induced by acid-adaptation. Such responses could potentially pose critical implications for food safety, challenging the efficacy of hurdle technologies. Therefore, the aim of this review is to summarize the effect of acid-adaptation on the cross-protection of foodborne pathogens, as well as to discuss in detail the molecular mechanisms for cross-protection between acid-adaptation and subsequent stresses. Additionally, we also discuss the current and future prospective of research on this topic with the knowledge gaps that remain present in the literature .

Cross-protection responses induced by acid-adaptation

Foodborne pathogens encounter several conditions in foods which may provide means by which they become acid-adapted (Álvarez-Ordóñez et al. 2009a). Many processes in food production cause a reduction of the pH, such as fermentation of a variety of foods (Jones, Price, and Breidt 2020), the addition of organic acids as preservatives (Bushell et al. 2018), and the use of organic acids as antimicrobial sprays in meats (Álvarez-Ordóñez et al. 2009a). However, during these processes, foodborne pathogens also encounter multiple stresses such as chemicals (e.g., salts and oxidants) and physical treatments (e.g., heat, suboptimal temperature, and pressure). Bacteria adapted to these stresses may survive or even proliferate under conditions that could have ordinarily eliminated them, a phenomenon known as cross-protection (Haberbeck et al. 2017) (Figure 1). In this part, the effect of acid-adaptation on the cross-protection of foodborne pathogens to food-associated stresses are discussed (Table 1).

Acid-adaptation and heat resistance

Foods are heated for many reasons, the most notable ones being to inactivate pathogenic and spoilage microorganisms (Sarjit et al. 2021). As a result, thermal processing is one of the most widely used methods in food processing for ensuring food safety and shelf-life extension. Undesirable changes also occur during thermal processing such as loss of vitamins, minerals, fresh appearance, flavor, and texture (Roobab et al. 2018). Thus, pasteurization at mild heat (45 – 60 °C) is increasingly preferred in food industry (with some exceptions such as canned food); although sometimes mild heat might not ensure efficient inactivation of microorganisms (Liao et al. 2020). However, previous studies implied the linkage between acid-adaptation and thermal resistance of several foodborne pathogens. In a study of Haberbeck et al. (2017), *Escherichia coli* and *E. coli* O157:H7 cells, which were acid-adapted at pH 5.5 with hydrochloric acid (HCl) overnight prior to thermal treatment, were significantly more resistant to subsequent thermal treatment at 58 °C compared to their non-adapted counterparts. The D_{58} values of acid-adapted cells were 3.08 ± 0.29 and 2.40 ± 0.12 at pH during thermal inactivation 6.2 and 7.0, respectively. On the other hand, the D_{58} values of non-adapted cells were 1.24 ± 0.07 and 2.02 ± 0.06 at pH during thermal inactivation 6.2 and 7.0, respectively. This study proves that cross-protection to heat may occur after acid-adaptation in a common bacterium like *E. coli*. Álvarez-Ordóñez et al. (2009b) found that acid-adaptation with different acids (acetic, citric, lactic, and HCl) at different pH values (6.4, 5.4, and 4.5) induced a resistance response to extreme pH conditions (pH 2.5) and to heat in *Salmonella* Typhimurium (50, 54, 58 °C) and *S.* Seftenberg (55, 58, 63 °C) in orange and apple juices. Acid-adapted *S.* Typhimurium displayed a 2-times increase in $D_{58°C}$-values compared to its non-adapted counterpart. However, cross-protection was stronger in *S.* Seftenberg, displaying $D_{58°C}$ -values (1.01 to 1.38 min) 10 times higher than those of its non-adapted counterpart (0.11 min). It is

Table 1. The effect of acid-adaptation on the cross-protection responses of foodborne pathogens to various stresses.

Acid-adaptation conditions	Cross-protection responses	Mediums	Strains	Degree of cross-protection		References
				Non-adapted D-values	Acid-adapted	
Overnight exposition at pH 5.5	Heat (58 °C)	LB broth	*Escherichia coli*, *Escherichia coli* O157:H7	1.24 – 2.02	2.40 – 3.08	Haberbeck et al. 2017
Long-term exposition up to pH 4.5 with different acids	Heat (50, 54, and 58 °C for *S.* Typhimurium) (55, 58, and 63 °C for *S.* Senftenberg)	BHI, orange and apple juices	*Salmonella* Typhimurium, *Salmonella* Seftenberg	*S.* Senftenberg apple juice: 0.43 (55 °C), 0.19 (56 °C, 0.025 (63 °C)	*S.* Senftenberg apple juice: 2.91 – 3.42 (55 °C), 0.79 – 1.14 (58 °C), 0.19 – 0.27 (63 °C)	Álvarez-Ordóñez et al. 2009b
Growth in the presence of glucose for 18 h	Heat (60 °C)	Tryptic soy broth	*Listeria monocytogenes*	0.53 – 1.16	0.52 – 0.76	Bayles 2004
Growth in the presence of glucose for 18 h	Heat (52, 56, and 60 °C)	Nutrient broth	*Salmonella* Enteritidis, *Salmonella* Typhimurium, *Salmonella* Bredeney	*S.* Enteritidis: 38.31 (52 °C), 5.23 (56 °C)	*S.* Enteritidis: 51.98 (52 °C), 7.79 (56 °C)	Malheiros et al. 2009
Long-term exposition up to pH 4.5 with HCl	Heat (63 °C)	Brain heart infusion	*Salmonella* Senftenberg	1.05 – 1.07	3.10 – 6.27	Álvarez-Ordóñez et al. 2009c
Long-term exposition up to pH 4.5 with different acids	Heat (58 °C)	Brain heart infusion	*Salmonella* Typhimurium	0.04 – 0.46	0.07 – 1.02	Álvarez-Ordóñez et al. 2008
Growth in the presence of glucose for 18 h	Heat (52, 54, and 56 °C)	Tryptic soy broth	*Escherichia coli* O157:H7, non-O157:H7 STEC	58.3 (52 °C), 11.3 (54 °C), 4.3 (56 °C)	116.5 (52 °C), 21.6 (54 °C), 6 (56 °C)	Ryu and Beuchat 1999
Growth in the presence of glucose for 18 h	Heat (52 and 54 °C)	Tryptic soy broth, apple cider, and orange juice	*Escherichia coli* O157:H7	In apple cider: 116.5 (52 °C), 22.6 (54 °C)	In apple cider: 84.7 – 94.3 (52 °C), 7.2 – 10.8 (54 °C)	Ryu and Beuchat 1998
Growth in the presence of glucose for 24 h	Heat (58, 62, and 65 °C)	Tryptic soy broth and meat serum	*Escherichia coli* O157:H7 and *Salmonella* spp.	*E. coli* O157:H7: 10.59 (58 °C), 1.38 (62 °C), 0.75 (65 °C). *Salmonella*: 6.44 (58 °C), 0.88 (62 °C), 0.95 (65 °C)	*E. coli* O157:H7: 22.46 (58 °C), 3.58 (62 °C), 1.02 (65 °C). *Salmonella*: 9.36 (58 °C), 1.66 (62 °C), 1.14 (65 °C)	Singh et al. 2010
Exposition to pH 5.3 with lactic acid or trisodium phosphate	Heat (54, 56, 58, and 60 °C)	Tryptic soy broth	*Salmonella* Enteritidis	11.48 (54 °C), 5.40 (56 °C), 2.24 (58 °C), 0.71 (60 °C)	13.11 – 13.27 (54 °C), 5.87 – 6.35 (56 °C), 2.33 – 2.41 (58 °C), 0.87 (60 °C)	Yang et al. 2014
Growth in the presence of glucose for 18 h and exposition at pH 5.5 with HCl for 30 min	Heat (50 °C) and freeze/thaw (−20/21 °C)	Tryptic soy broth	*Aeromonas hydrophila*	2.7 – 3 (50 °C), 0.71 – 0.98 (−20 °C/21 °C)	2.6 – 2.8 (50 °C), 0.75 – 0.79 (−20 °C/21 °C)	Isonhood et al. 2002
Long-term exposition up to pH 4.5 with different acids	Alkali (1.5, 2.0, or 2.5 % trisodium phosphate (TSP); NaOH pH 10.0, 10.5, and 11.0)	Brain heart infusion	*Salmonella* Typhimurium	150.2 (pH 10); 31.5 (pH 10.5); 5.09 (pH 11)	243.6 – 333.4 (pH 10); 51.5 – 60.3 (pH 10.5); 7.94 – 9.86 (pH 11)	Álvarez-Ordóñez et al. 2011
Growth in the presence of glucose for 24 h	Heat (62 and 65 °C)	Tryptic soy broth and meat serum	*Escherichia coli* O157:H7 and *Salmonella* spp.	Stored at 4 °C *E. coli* O157: −1.97 – 4.60 (62 °C); 0.91 – 1.58 (65 °C). *Salmonella*: 1.98 – 4.29 (62 °C); 0.82 – 1.38 (65 °C)	Stored at 4 °C *E. coli* O157: 2.20 – 2.88 (62 °C); 0.80 – 1.27 (65 °C). *Salmonella*: 1.93 – 2.98 (62 °C); 0.73 – 1.23 (65 °C)	Singh et al. 2006
Exposition up to pH 4.5 with acetic, ascorbic, citric, lactic, malic, and hydrochloric acid	Non-thermal atmospheric plasma (10L/min)	Brain Heart Infusion broth	*Salmonella* Typhimurium and *Salmonella* Enteritidis	*S.* Typhimurium: 0.68 – 1.38 *S.* Enteritidis: 0.73 – 1.23	*S.* Typhimurium: 1.16 – 1.67 *S.* Enteritidis: 0.99 – 1.55	Calvo et al. 2017
Exposition at pH 5.0 or 5.5 with HCl for up to 10 h		Tryptic soy broth	*Vibrio vulnificus*	Strain 304C ∼1.76 (47 °C); ∼0.79	Strain 304C ∼1.75 – 1.95 (47 °C);	Bang and Drake 2005

(*continued*)

Table 1. Continued.

Acid-adaptation conditions	Cross-protection responses	Mediums	Strains	Degree of cross-protection		References
				Non-adapted D-values	Acid-adapted	
	Heat (47 °C), freeze/thaw (−20/21 °C), and cold (5 °C)			(−20 °C/23 °C); ∼1.4 (5 °C)	∼0.78 – 0.9 (−20 °C/ 23 °C); ∼1.4 – 1.65 (5 °C)	
Exposition to pH 5.0 with HCl for 1, 4, or 18 h	Ultrasound (0.4, 7.5, and 37.5 μm)	Tryptic soya broth, model orange juice, and model apple juice	*Escherichia coli* and non-STEC O157:H7	Amplitude 7.5: 2.33	Amplitude 7.5: 2.12 (1 h); 2.43 (4 h); 2.98 (18 h)	Patil et al. 2009
Exposition at pH 5.5 for 1 h	Heat (55 – 63 °C)	Tryptic soy broth	*Listeria monocytogenes*	34.36 (55 °C), 11.96 (57 °C), 7.37 (59 °C), 3.74 (61 °C), 2.42 (63 °C)	45.25 (55 °C), 17.83 (57 °C), 7.47 (59 °C), 3.80 (61 °C), 2.40 (63 °C)	Pongkanpai, Makakarnchanakul, and Garnjanagoonchorn 2013
				Survival		
Exposition at pH 5.5 with HCl for 90 min	Heat (47 °C), cold (4 and −20 °C), ethanol (8%), high salt (20% NaCl), and hydrogen peroxide (20 ppm)	Tryptic soy broth	*Vibrio parahaemolyticus*	0.2%, 1.5%, and 0.2% (47 °C for 50 min). 10.4% (8% ethanol). 1,5% (20% NaCl). 4.92% (20 ppm H_2O_2)	4.2%, 3.1%, and 3.0% (47 °C for 50 min). 32.7% (8% ethanol). 3.5% (20% NaCl). 1.2% (20 ppm H_2O_2)	Chiang et al. 2014
Growth in the presence of glucose for 18 h	Heat (52 and 60 °C)	Nutrient broth	*Salmonella* Enteritidis	∼500 CFU/mL (52 °C, 180 min). ∼3000 CFU/ mL (60 °C, 2.5 min)	∼6000 CFU/mL (52 °C, 180 min). ∼10000 CFU/ mL (60 °C, 2.5 min)	Ritter et al. 2014
Exposition at pH 5.5 with HCl for 120 min	Heat (49 °C), cold (4 and −20 °C), and hydrogen peroxide oxidation (5mM)	Tryptic soy broth	*Bacillus cereus*	0.20% (49 °C, 25 min). 36.1% (4 °C, 5 days). 0.10% (−18 °C, 4 days)	8.30% (49 °C, 25 min). 1.2% (4 °C, 5 days). 0.35% (−18 °C, 4 days)	Chen et al. 2009a
Exposition at pH 5.8 with HCl	Heat (50 °C), salt (2.5 M NaCl), polymyxin B and crystal violet (5000 mg/ L each), and lactoperoxidase system	Medium E and brain heart infusion	*Salmonella* Typhimurium	∼2% (50 °C, 20 min). ∼0.02% (2.5 M NaCl, 6 days). ∼0.9% (25 mg crystal violet, 20 min). ∼0.8% (10 mg polymyxin B sulfate, 20 min)	∼30% (50 °C, 20 min). ∼10% (2.5 M NaCl, 6 days). ∼40% (25 mg crystal violet, 20 min). ∼6% (10 mg polymyxin B sulfate, 20 min)	Leyer and Johnson 1993
Exposition up to pH 5.0 with HCl	Heat (45 °C) and low salinity	Luria-Bertani	*Vibrio parahaemolyticus*	∼15% (45 °C, 20 min). ∼42% (low salinity 10 min)	∼34% (45 °C, 20 min). ∼65% (low salinity 10 min)	Wong et al. 1998
Overnight exposition to pH 5.4	Nisin (up to 1.5 μg/mL)	Brain heart infusion	*Listeria monocytogenes*	53% (0.3 μg/mL, 90 min)	70% (0.3 μg/mL, 90 min)	Okereke and Thompson 1996
Exposition to pH 5.0 with lactic acid for 1 h	Different disinfectants	Tryptic soy broth	*Listeria monocytogenes*	2.3 log CFU/mL (200,000 ppm ethanol, 60 min)	4.2 log CFU/mL (200,000 ppm ethanol, 60 min)	Dhowlaghar et al. 2019
Exposition to pH 5.3 with HCl	Heat (47 °C), crystal violet (30 μg/mL), bile (5%), and deoxycholic acid (0.1%)	Luria-Bertani broth	*Vibrio parahaemolyticus*	200-fold decrease after 10 min (47 °C). 12% (crystal violet, 10 min). 10% (bile, 10 min). 10% (deoxycholic acid, 10 min)	200-fold survivors after 10 min (47 °C). 80% (crystal violet, 10 min). 50% (bile, 10 min). 60% (deoxycholic acid, 10 min)	Koga et al. 1999
Exposition up to pH 4.5 with HCl for up to 4 h	Heat (50 °C), cold (−20°), and salt (8%)	Luria-Bertani	*Salmonella* Enteritidis	50% (50 °C, 20 min). 2% (8% NaCl, 1 h). 80% (4 °C, 3 days). 15% (−20 °C, 3 h).	100% (50 °C, 20 min). 10% (8% NaCl, 1 h). 100% (4 °C ,3 days). 35% (−20 °C, 3 h)	Ye et al. 2019
Growth in the presence of glucose for 15 h	Osmosis (A_w 0.91 with NaCl or KCl)	Tryptic soy broth	*Salmonella* Typhimurium	NaCl and KCl, 2 days: 0.02% and 0.05% respectively	NaCl and KCl, 2 days: 0.08% and 1.5% respectively	Greenacre and Brocklehurst 2006

Exposition at pH 4.5 with HCl for 1 h	Freeze/thaw (−20/30 °C) and high hydrostatic pressure (up to 400 MPa)	Brain heart infusion	*Listeria monocytogenes*	∼0.01% (350 MPa, 8 min)	∼80% (350 MPa, 8 min)	Wemekamp-Kamphuis et al. 2004
Exposition at pH 5.5 with lactic acid	Osmosis (20% NaCl)	Trivett and Meyer medium	*Listeria monocytogenes*	Strain C882: 0.37% (20% NaCl)	Strain C882: 8.0% (20% NaCl)	Faleiro et al. 2003
Exposition at pH 5.5 for 2 h	Ethanol (20%) and salt (20% NaCl)	Tryptic soy broth	*Bacillus cereus*	0.24% (20% ethanol, 4 h). 18.5% (20% NaCl, 4 h)	0.04% (20% ethanol, 4 h). 3.5% (20% NaCl, 4h)	Chen et al. 2009b
Exposition at pH 5.5 with lactic acid for 2 h	CO_2 (25%)	Tryptic soy broth and ready-to-use packaged vegetables	*Listeria monocytogenes* and *Listeria innocua*	*L. monocytogenes:* ∼7.3 Log CFU per plate (25% CO_2, 12 days)	*L. monocytogenes:* ∼8.1 Log CFU per plate (25% CO_2, 12 days)	Francis and O'Beirne 2001
Exposition to pH 4.5 – 5.0	Ethanol (17.5%), hydrogen peroxide (0.1%), NaCl (25%), and starvation	Trypticase soy broth	*Listeria monocytogenes*	∼2.1 log CFU/mL (H_2O_2, 3 h). ∼1.0 log CFU/mL (ethanol, 8 h)	∼6.1 – 8.6 log CFU/mL (H_2O_2, 3 h). ∼3.25 log CFU/mL (ethanol, 8 h).	Lou and Yousef 1997
Exposition to pH 5.5 and 4.5 for 4 and 24 h.	Non-thermal plasma (50 W for 30 s)	Nutrient broth	*Escherichia coli* and *Staphylococcus aureus*	*E. coli:* 8.40 log CFU/mL (24 h). *S. aureus:* 8.30 log CFU/mL (24 h)	*E. coli:* 8.43 log CFU/mL (24 h). *S. aureus*: 8.27 log CFU/mL (24 h)	Liao et al. 2018
Exposition to pH 5.0 for 1 h	Lauric arginate (50 ppm)	Tryptic soy broth, milk, and carrot	*Listeria monocytogenes*	∼1.6 log CFU/mL (20 min)	∼4.1 log CFU/mL (20 min)	Shen et al. 2015
Exposition to pH 5.5 with lactic acid for 1 h	Heat (54 °C), NaCl (2.5 M), ethanol (15%), crystal violet (100 mg/L), and hydrogen peroxide (180 mM); virulence	Tryptone soy broth	*Listeria monocytogenes*	∼1% (100 mg/L crystal violet, 40 min). ∼30% (15% ethanol, 60 min)	∼50% (crystal violet, 40 min). ∼80% (15% ethanol, 60 min)	O'driscoll, Gahan, and Hill 1996
				Population reduction		
Growth in the presence of glucose for 20 h	UVA + gallic acid (30 min + 10 mM)	Tryptic soy broth	*Escherichia coli* O157:H7	Reduction of 4.4 log CFU/mL	Reduction of 2.2 log CFU/mL	Wang et al. 2019
Exposition up to pH 5.0 with acetic acid up to 7 h	Cold (4 and 20 °C)	Trypticase soy broth	*Salmonella* Enteritidis	4.57 log CFU/mL decrease compared to acid-adapted (4 °C, 12 day)		Xu et al. 2008
Exposition to pH 5.5 with HCl for 4 h	Cold (5 °C)	Tryptic soy broth, skim milk broth, fermented milk, and skim milk	*Salmonella* Typhimurium	Population reduction: Skim milk: 0.43 log CFU/mL. Yogurt: 1.34 log CFU/mL. Fermented milk: 1.05 log CFU/mL	Population reduction: Skim milk: 0.15 log CFU/mL. Yogurt: 0.60 log CFU/mL. Fermented milk: 0.30 log CFU/mL	Shen et al. 2007
Exposition to pH 5.0 with HCl for 18 h	222-nm KrCl excilamp (197 – 1,773 mJ/cm^2)	Tryptic soy broth, apple juice, and PBS	*Salmonella* Typhimurium and *Escherichia coli* O157:H7	*S.* Typhimurium: 3.65 – 6.65 log reduction (197 – 1,773 mJ/cm$_2$). *E. coli* O157:H7: 3.11 – 6.84 (197 – 1,773 mJ/cm$_2$)	*S.* Typhimurium: 2.01 – 5.29 log reduction (197 – 1,773 mJ/cm$_2$). *E. coli* O157:H7: 2.20 – 5.51 (197 – 1,773 mJ/cm$_2$)	Kang and Kang 2019
Exposition to pH 5.0 with HCl	X-ray (up to 1 kGy)	Tryptic soy broth and apple juice	*Escherichia coli* O157:H7 and *Salmonella* Typhimurium	*E. coli* O157:H7: 1.41 – 8.02 log reduction (0.2 – 1.0 kGy). *S.* Typhimurium: 1.03 – 3.87 log reduction (0.2 – 1.0 kGy)	*E. coli* O157:H7: 1.22 – 5.48 log reduction (0.2 – 1.0 kGy). *S.* Typhimurium: 1.21 – 3.98 log reduction (0.2 – 1.0 kGy)	Lim and Ha 2021
Growth in the presence of glucose for 18 h	Cold (4 °C)	Tryptic soy broth	*Shigella flexnerii*	6 log CFU/mL (4 °C, 144 h)	2.5 log CFU/mL (4 °C, 144 h)	Tetteh and Beuchat 2003
				Population		
Exposition to pH 5.5 with different acids for 1 h	Nisin	Tryptic soy broth and M17G broth	*Listeria monocytogenes*	∼1.3 log CFU/mL (2 days)	∼2.4 log CFU/mL (2 days)	Bonnet and Montville 2005
				Minimum inhibitory concentration (MIC)		
Exposition up to pH 5.0 with lactic acid for 30 min	Antibiotics (streptomycin, gentamycin, ampicillin, penicillin, tetracycline,	Potassium phosphate buffer	*Listeria monocytogenes*	Streptomycin: 8; gentamycin: 0.125; ampicillin: 0.125	Streptomycin: 0.5 – 4-fold increase; gentamycin: 2.1 – >4-fold increase;	Al-Nabulsi et al. 2015

(*continued*)

Table 1. Continued.

Acid-adaptation conditions	Cross-protection responses	Mediums	Strains	Non-adapted D-values	Degree of cross-protection Acid-adapted	References
	doxycycline, vancomycin, ciprofloxacin, enrofloxacin)				ampicillin: 0.5 – >4-fold increase	
Exposition to pH 3.5 with lactic acid for 30 min	Streptomycin, gentamicin, kanamycin, neomycin, tetracycline, doxycycline, tilmicosin, florfenicol, amplicillin, amoxicillin, vancomycin, ciprofloxacin, and enrofloxacin	Potassium phosphate buffer	*Cronobacter sakazakii*	Neomycin: 100; tetracycline: 40	Neomycin: 0.5 – 2-fold increase; tetracycline: 0.5 – 4-fold increase	Al-Nabulsi et al. 2011
				Lethality		
Exposition at pH 5.5	Heat (50 °C)	J-Broth	*Bacillus cereus*	4.28 – 5.21 log (N_0/N)	2.69 – 3.51 (N_0/N)	Le Lay et al. 2015

also noteworthy that under several conditions, acid-adapted *S.* Typhimurium displayed higher D-values than those of non-adapted *S.* Seftenberg. These results show that different serotypes under different conditions may respond different to stress. In another study carried out by Singh et al. (2010), *E.coli* O157:H7 and *Salmonella* spp. cells were acid-adapted by growing in culture medium with 1% glucose. The presence of glucose in the culture medium allows the production of organic acids, which significantly decreases the final pH of the culture medium. D-values of acid-adapted *E. coli* O157:H7 cells (22.46, 3.58, and 1.02 min at 58, 62, and 65 °C, respectively) in meat serum were higher than those of non-adapted counterparts (10.59, 1.38, and 0.75 min at 58, 62, and 65 °C, respectively). Increase in D-values was observed in acid-adapted from non-adapted *Salmonella* in meat serum at 58 and 62 °C but not at 65 °C. It seems that acid-adaptation did not protect *Salmonella* in meat serum at the temperature of 65 °C. The cross-protection to heat in *Listeria monocytogenes*, a pathogen with particular acid resistance, has also been reported. Pongkanpai, Makakarnchanakul, and Garnjanagoonchorn (2013) reported that acid-adapted (pH 5.5 for 1 h) *L. monocytogenes* cells demonstrated increased tolerance to thermal stress at 55 – 63 °C. Spore forming pathogens, such as *Bacillus cereus*, have also shown thermal cross-protection (50 °C) induced by acid-adaptation and it is probably part of the activation of heat shock protein coding genes after growth at pH 5.5 (Le Lay et al. 2015). Moreover, previous studies have shown that the pH value of *B. cereus* would decrease around 1.2 prior to undertaking sporulation, reducing the proton concentration difference inside and outside the membrane. This allows the pathogen to maintain pH homeostasis to increase resistance (Duport, Jobin, and Schmitt 2016).

Acid-adaptation and cold resistance

Low temperature is frequently used for the preservation of foods. It slows metabolic processes of microbial cells present in food. However, there is evidence that acid-adaptation may influence the resistance of microorganisms to cold stress, such as *S.* Enteritidis, *E. coli*, *Vibrio vulnificus*, and *L. monocytogenes* (Ye et al. 2019). Meaning that, foodborne pathogens which have developed cross-protection to cold as a result of acid-adaptation, may keep growing and reproducing under cold conditions. Tetteh and Beuchat (2003) reported that *Shigella flexnerii* cells are able to survive at 4 °C regardless of pH. However, acid-adapted *S. flexnerii* cells (grown in medium supplemented with 1% glucose at 37 °C for 18 h) decreased by 2.5 $\log_{10}$ colony-forming unit/mL (CFU/mL) compared with 6 $\log_{10}$ CFU/mL reduction in non-adapted cells when incubating at 4 °C for 144 h, probably due to non-adapted cells entering to a non-culturable state. In a study of Shen, Yu, and Chou (2007), acid-adapted (pH 5.5 adjusted with 6 N HCl) *S.* Typhimurium showed higher resistance to refrigerated temperature (5 °C) compared with non-adapted counterpart in fermented milk (yogurt, pH 4.20 – 4.23). Similarly, Xu, Lee, and Ahn (2008) reported that acid-adapted (pH 5.0 adjusted with acetic

acid) *S.* Enteritidis developed cross-protection against cold stress (4 and 20 °C) at pH 4.0. Acid-adapted pathogens may also survive in extreme low temperature. As an example, Chen, Chiang, and Chou (2009a) reported that acid-adaptation (pH 5.5) increased the survival of mesophilic *B. cereus* cells in vegetative state during storage at −18 °C compared with non-adapted cells. Meanwhile, acid-adapted cells showed decreased survival at 4 °C compared with non-adapted cells. It is interesting to observe that acid-adapted *B. cereus* respond different to cold stress at 4 °C as compared with other foodborne pathogens such as S. Typhimurum or *S. flexnerii*. Moreover, acid-adapted *B. cereus* was cross-protected against frozen storage temperature (−18 °C), probably due to the induction of cold shock proteins induced by the cross-protection response (Gottesman 2018). The effect of acid-adaptation on freeze/thaw resistance of pathogens has also been studied. Bang and Drake (2005) reported that acid-adaptation at pH 5.0 adjusted with HCl increased freeze/thaw (−20/21 °C) resistance in one of two strains of *V. vulnificus*. This study demonstrates that different bacteria strains may develop different cross protection responses. The freeze/thaw-resistant *V. vulnificus* strain was benefited by the induction of specific protective proteins which rendered cross protection to freeze/thaw stress. Similarly, Wemekamp-Kamphuis et al. (2004) reported freeze/thaw (−20/30 °C) cross-protection response induced by acid exposure of *L. monocytogenes* at pH 4.5 adjusted with HCl. In this study, two *L. monocytogenes* strains, a wild-type and a Δ*sigB* mutant were exposed to acidic (pH 4.5) and neutral conditions. Low pH was adjusted with HCl. After five freeze/thaw cycles, the level of survival of wild-type strain was three-fold higher than that of the Δ*sigB* mutant, suggesting that the cross-protection against freeze/thaw stress was mainly by the expression of σ^B-regulated proteins and alteration of membrane fatty acids. Csp1 and Csp3, which are two cold shock proteins were upregulated in the wild-type and were reduced in the Δ*sigB* mutant. In acid-adapted cells, the levels of C14:0 and C16:0 fatty acids were significantly increased, whereas the levels of C18:0 decreased in the cell membrane. Resulting in alteration of cell membrane and thus, providing protection against acid and low temperature.

Acid-adaptation and osmosis (salt) resistance

Acid fermentation combined with salting remains one of the most historical methods of preservation for a variety of foods, especially fresh vegetable (Tamang 2010). The addition of salts allows the reduction of water activity and increases the osmotic pressure. Therefore, the cross-protection between acid-adaptation by low pH and osmosis resistance by decreased water activity of foodborne pathogens is a main food safety issue. These conditions are present in fermented foods. In a study of (Chiang et al. 2014), *Vibrio parahaemolyticus* cells were acid-adapted at pH 5.5 adjusted with 10 N HCl and incubated at 37 °C for 90 min. Then, acid-adapted and non-adapted cells were transferred to 20% (w/v) sodium chloride (NaCl). After 240 min, acid-adapted cells (strain 690) showed significant higher percentage of survival than non-adapted cells, which proved that acid-adaptation induced cross-protection against osmotic shock (20% NaCl). Interestingly, osmoadaptation in mild osmotic conditions (3.5% NaCl) also induced cross-protection against acid shock (pH 3.5 adjusted with lactic acid), showing an interplay behavior between acid-tolerance and osmotolerance in *L. monocytogenes*. Moreover, the results of this study suggest that the use of hurdles such as acid and salt, which are believed to be effective in controlling pathogens growth, may not always be effective for some cross-protected foodborne pathogens (e.g., *L. monocytogenes*). For instance, in 58 cases of listeriosis outbreaks reported from 1998 to 2014 in the USA, a total of 17 (30%) were linked to soft cheese (Jackson et al. 2018). Several listeriosis outbreaks associated with different types of cheese have been reported in Europe (Melo, Andrew, and Faleiro 2015). Soft cheeses pose a major concern to food safety for they are the leading source of listeriosis outbreaks, due to the abilities of *L. monocytogenes* to overcome hurdles (Melo, Andrew, and Faleiro 2015). A major outbreak of *B. cereus* linked to fermented black beans occurred in China in 2006 (Zhou et al. 2014). Two consecutive outbreaks of *E. coli* O6 linked to fermented vegetable kimchi occurred in schools in South Korea in 2013 and 2014 (Shin et al. 2016).

Greenacre and Brocklehurst (2006) found that lactic acid (pH 5.5) failed to protect *S.* Typhimurium cells against osmotic stress. However, acetic acid (pH 5.5) provided protection against NaCl and potassium chloride (KCl) stress. The different cross-protection phenotypes produced by acetic and lactic acid is possibly related to the ability of the acid to enter the cell membrane. Acetic acid is more lipophilic than lactic acid, so may enter the cell membrane easier and cause more intracellular effects. The difference may also be attributed to the different acid dissociation constant (pK_a) of each acid. At 25 °C, the pK_a of acetic and lactic acid are 4.76 and 3.86, respectively (Lower 2020). At pH 5.5, acetic acid is slightly more undissociated than lactic acid, hence increasing its ability to penetrate the cell membrane (Eklund 1983). Meanwhile, in the study by Zorraquino et al. (2016), acid-adaptation (pH 5.5) of *E. coli* provided cross-protection against high levels of NaCl (0.3 M). The different outputs of these studies suggest that different acids may induce different responses in different bacteria and even strains. These results suggest the food safety risks for food industry, especially traditional fermented foods, where acidic pH and salt are used for preservation. Moreover, these results point to a need to evaluate whether the combinations of acid and salt (hurdle) are sufficient to control pathogens.

Acid-adaptation and antibiotic resistance

In agricultural practices, the use of antibiotics in animal feeds generally kills a certain population of microorganisms including animal pathogens but encourage other resistant ones to grow (Bhunia 2018). Residues of antibiotic and antibiotic-resistant bacteria could end up in foodstuffs from animal origin and transmitted to humans (Zhang et al. 2016).

Moreover, some studies have shown that acid-adaptation may induce cross-protection to antibiotics in foodborne pathogens. Al-Nabulsi et al. (2015) reported that *L. monocytogenes* strains (one American Type Culture Collection (ATCC) strain and two isolates from meat and dairy) developed resistance to several antibiotics (streptomycin, gentamycin, ampicillin, penicillin, tetracycline, doxycycline, vancomycin, ciprofloxacin, and enrofloxacin) induced by acid-adaptation at pH 5.0 adjusted with lactic acid. Before acid-adaptation the minimum inhibitory concentrations (MICs) of streptomycin, gentamycin, ampicillin, penicillin, tetracycline, doxycycline, vancomycin, ciprofloxacin, and enrofloxacin for *L. monocytogenes* ATCC strain were 8, 0.125, 0.125, 0.06, 0.25, 0.06, 0.125, 0.5, and 0.25 μg/mL, respectively; for *L. monocytogenes* meat strain were 4, 1, 0.125, 0.125, 0,25, 0.06, 0.25, 0.5, and 0.125 μg/mL, respectively; and for *L. monocytogenes* dairy strain were 8, 0.25, 0.125, 0.125, 0.06, 0.06, 1, 0.25, and 0.06 μg/mL, respectively. Acid-adaptation increased the MICs of antibiotics against all strains by 0.5 to >4-fold. All three strains displayed moderate resistance to penicillin and two strains became more resistant to streptomycin than the third strain became moderately resistance. In contrast, the strain that showed moderate resistance to streptomycin, became more resistant to floxacin than the other two strains. It is interesting to note that even strains within the same bacteria species may respond different between each other, because of different phenotypic characteristics mainly due to different origins of each strain. *L. monocytogenes* also developed resistance to nisin following acid-adaptation at pH 5.5 (Bonnet and Montville 2005) tested different acids (HCl, acetic and lactic acid) to induce acid tolerance response in *L. monocytogenes*. Cells were acid-adapted at pH 5.5 then challenged in culture medium at pH 3.5 with the same acid. Only lactic acid induced a pronounced acid tolerance response. Acids enter the cell membrane mainly in the undissociated form. At pH 5.5, HCl (a strong acid) is dissociated, while acetic and lactic acids (weak acids) are undissociated. Thus, an equilibrium of the associated and dissociated forms occurs The authors explained that, the nominal molar concentration of acetic acid in tryptic soya broth with yeast is higher than lactic acid at pH 3.5; therefore, the high concentration of acetic acid in the medium (pH 3.5) would result in free diffusion of associated form across the membrane overwhelming the protection that may have been induced by this acid during the adaptation step (pH 5.5). Lactic-acid-tolerant cells developed cross-protection against nisin in fermented medium (pH 5.7; in the presence of nisin-producing *Lactococcus lactis*). As a result, lactic-acid-tolerant *L. monocytogenes* survived to the pH of the medium and also to the presence of nisin. Al-Nabulsi et al. (2011) also observed that *Cronobacter sakazakii* displayed resistance to enrofloxacin, ampicillin, and amoxicillin after exposition to pH 3.5 adjusted with lactic acid in potassium phosphate buffer. Sub-lethal acid conditions in food preservation systems may induce antibiotic cross-protection in foodborne pathogens, posing a potential threat to food safety.

Acid-adaptation and disinfectant resistance

Disinfectants or sanitizers are commonly used in food industry to reduce the surface population of viable microorganisms and prevent surface microbial growth in food or processing equipment (Holah 2013). Because the present review focuses on acid-adaptation and cross-protection to subsequent stresses (stresses different to acid), acid sanitizers are excluded in this section. Some studies have reported the relationship between disinfectant resistance and acid-adaptation. Dhowlaghar et al. (2019) tested acid-adapted (pH 5.0 with lactic acid) *L. monocytogenes* in lethal concentrations of disinfectants in broth and water. The authors found that acid-adapted *L. monocytogenes* cells exhibited higher survival against lethal concentrations of sodium hydroxide (NaOH), potassium hydroxide (KOH), ammonium hydroxide (NH_4OH), ethanol, isopropanol, quaternary ammonium compound 1 (QAC-1), and quaternary ammonium compound 2 (QAC-2), but were more susceptible to hydrogen peroxide (H_2O_2) compared with non-adapted cells. The susceptibility of acid-adapted *L. monocytogenes* to H_2O_2 may be linked to downregulation of transcription factor *OxyR*. Similar survival patterns were observed in both water and broth models, suggesting that the effect of acid-adaptation in disinfectant resistance response of *L. monocytogenes* was unaltered by the presence of nutrients. Similarly, Chiang et al. (2014) reported that acid-adapted (pH 5.5 adjusted with HCl) *V. parahaemolyticus* showed increased resistance to ethanol and susceptibility to H_2O_2. However, opposite observation was also reported by Lou and Yousef (1997) in which acid-adapted (pH 4.5–5.0 with HCl) *L. monocytogenes* cells showed increased resistance to lethal concentration of H_2O_2 compared with non-adapted cells. Unlike these previous studies, the susceptibility of *B. cereus* to H_2O_2 was unchanged after acid-adaptation at pH 5.5 with HCl (Chen, Chiang, and Chou 2009a). Thus, these results suggest that cross-protection response of pathogens to H_2O_2 may vary with strains and adaptation conditions.

Acid-adaptation and non-thermal technology resistance

Thermal processing adversely affects sensory, nutritional, and functional properties of foods (Wu et al. 2020). For instance, the increasing demand of consumers for fresh-like and nutritious food products without compromising food safety has ushered the development of non-thermal food processing technologies (Calvo et al. 2017). Non-thermal technologies such as ultrasound, UV, pulsed light, cold plasma, pulsed electric field, and high-pressure processing inactivate foodborne pathogens at low temperature while ensuring the quality of foods (Van Impe et al. 2018). However, foodborne pathogens have managed to survive under non-thermal treatments (Cebrián, Mañas, and Condón 2016). The cross-protection of acid-adaptation and resistance to non-thermal treatments in foodborne pathogens has been reported in recent years. Kang and Kang (2019) reported that acid-adapted (pH 5.0 adjusted with HCl) *S.* Typhimurium and *E. coli* O157:H7 cells exhibited significantly higher D_{5d} values compared with non-adapted

Table 2. Some mechanisms in foodborne pathogens for acid-adaptation and cross-protection to other stresses.

Mechanism	Strains	Acid	Cross-protection	References
GAD system	*Listeria monocytogenes*	Hydrochloric acid	High hydrostatic pressure and freeze	Wemekamp-Kamphuis et al. 2004
Protection or repair of molecules	*Salmonella* Enteritidis	Glucose fermentation	Heat	Ritter et al. 2014
Protection or repair of molecules	*Salmonella* Typhimurium and *Salmonella* Bredeney	Glucose fermentation	Heat	Malheiros et al. 2009
Protection or repair of molecules	*Bacillus cereus*	Hydrochloric acid	Ethanol and salt	Chen et al. 2009b
Sigma factor	*Salmonella* Enteritidis	Hydrochloric acid	Heat, cold, and salt	Ye et al. 2019
Sigma factor	Non-O157:H7 STEC and STEC O157:H7	Pineapple juice	cold	Kim et al. 2016
Alteration of cell membrane	*Salmonella* Enteritidis	Lactic acid and trisodium phosphate	Heat	Yang et al. 2014
Alteration of cell membrane	*Salmonella* Typhimurium	Acetic, citric, lactic, and hydrochloric acid	Heat	Álvarez-Ordóñez et al. 2008
Alteration of cell membrane	*Salmonella* Seftenberg	Hydrochloric acid	Heat and cold	Álvarez-Ordóñez et al. 2009c
Alteration of cell membrane	*Vibrio parahaemolyticus*	Hydrochloric acid	Heat, crystal violet, bile, and deoxy cholic acid	(Koga et al. 1999
Alteration of cell membrane	*Listeria monocytogenes*	Potassium lactate and sodium diacetate	nisin and ε-polylysine	Kang et al. 2015

cells following 222-nm krypton-chlorine (KrCl) excilamp treatment immediately (5 s) after being inoculated in apple juice and phosphate-buffered saline (PBS). The pathogens in the apple juice exhibited higher D_{5d} values than those in PBS due to the UV-absorbing characteristics of apple juice. Patil et al. (2009) found that *E. coli* and non-Shiga toxin-producing *E. coli* (STEC) O157:H7 cells, acid-adapted at pH adjusted with HCl for 18 h, developed increased resistance to ultrasound treatment at 37.5 µm amplitude in culture broth, orange and apple juices. Non-adapted cells showed sensitivity to treatment at 7.5 and 37.5 µm amplitude, which indicates that long-term acid-adaptation of 18 h provided *E. coli* and STEC O157:H7 cross-protection to ultrasound. Wemekamp-Kamphuis et al. (2004) found that acid-adapted (pH 4.5 adjusted with HCl) *L. monocytogenes* cells developed cross-protection against high hydrostatic pressure (300 – 350 MPa) as compared with non-adapted cells. Thus, increasing the risk of overestimating the lethal effect of high hydrostatic pressure treatment. Liao et al. (2018) found that long-term (24 h) acid-adapted (pH 5.5) *Staphylococcus aureus* cells developed resistance to non-thermal plasma challenge compared with non-adapted cells. Contrary to short-term adaptation (4 h) which showed no effect on the resistance to non-thermal plasma. Similarly, Calvo et al. (2017) reported that stress adaptation (up to 2 h), including acid-adaptation achieved with different acids (HCl, acetic, ascorbic, citric, lactic, and malic acid) at different pH (6.4, 5.4, and 4.5), had a minor impact on non-thermal plasma resistance in *S.* Typhimurium and *S.* Enteritidis. It seems that pathogens require enough time for induction of cross-protection toward non-thermal treatments. Therefore, it is indispensable to consider the cross-protection related to acid-adaptation of foodborne pathogens, due to the possibility of overestimating the antimicrobial effects of non-thermal treatments on foodborne pathogens. Especially for fermented and acidic foods, or meat products, which are commonly sprayed with organic with the purpose of decontaminate bovine carcasses or chicken skin in slaughterhouses and meat processing plants, especially in the USA and Canada (Burin, Silva, and Nero 2014; Zaki, Mohamed, and El-Sherif 2015). These foods rely on non-thermal processing technology to keep high quality while assuring food safety.

Mechanisms for cross-protection between acid-adaptation and resistance to other stresses

Low pH can affect cellular components such as proteins, lipids, and nucleic acids, and cellular states such as the level of proton motive force, thus it is experimentally challenging to disentangle the consequences of these effects (De Biase and Lund 2015). The constant necessity for bacteria to adapt to a variety of stresses has forced the development of complex regulatory networks that respond to changes in the environment (Hu et al. 2020). The mechanisms by which foodborne pathogens respond to acid-adaptation and the subsequent cross-protection to other stresses have been reported in previous studies (Table 2). Moreover, evidence of multiple acid tolerance mechanisms in a single bacterial species has been reported previously (Foster 2001). This shows that acid-adapted foodborne pathogens may also utilize multiple mechanisms for cross-protection against other stress or multiple stresses. Here, an overview of the mechanisms known so far is provided (Figure 2).

Sigma factors

Sigma factors are one of the first mechanisms of gene transcription in bacteria that has been discovered. Its discovery dates back to 1969 when the group of Ekhardt Bautz and the group of Joshua Dunn published an article together (Burgess et al. 1969). Since then, sigma factors are being studied and are well-known transcription factors that reversibly bind ribonucleic acid polymerase (RNAP) to promote and mediate transcription of all genes through a primer-independent ribonucleic acid (RNA) synthesis in bacteria (Davis et al. 2017). Thus, sigma factors are responsible for the transcription of genes involved in tolerance to diverse stresses. It is a general mechanism, which means that it might be involved in other mechanisms of cross-protection

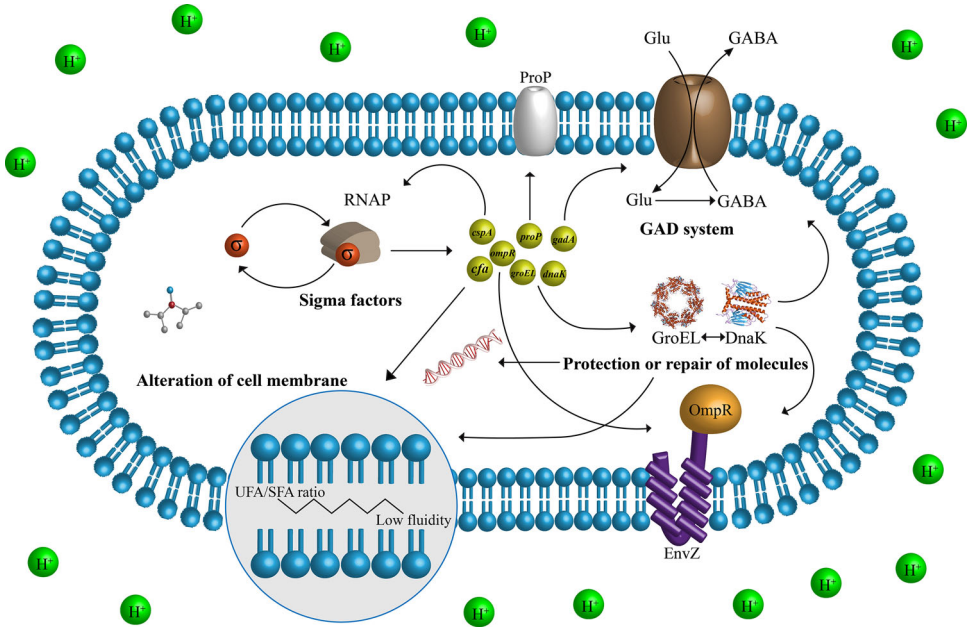

Figure 2. Relationship among known molecular mechanisms of acid-adaptation and cross-protection response in foodborne pathogens. Under acidic conditions, sigma factors are the main regulators of stress-related genes, which include genes that encode proteins involved in the alteration of cell membrane, osmoprotection, GAD system, GroEL/DnaK system, and OmpR/EnvZ system. The systems involved in protection or repair of molecules, protect or repair molecules such as DNA, membrane, organelles, and proteins; the latter, includes proteins that are involved in other mechanisms of cross-protection.

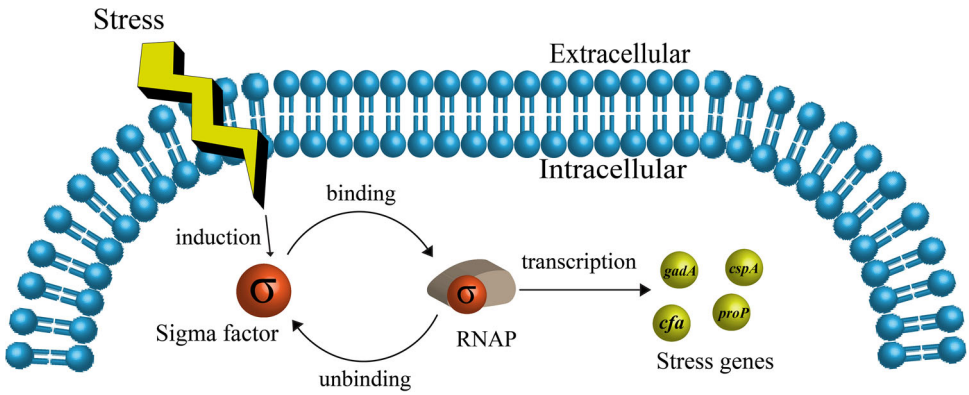

Figure 3. Induction of Sigma factor (σ) and transcription of genes in foodborne pathogen bacterial cell following acid stress.

(Liao et al. 2020). Previous studies suggested that the alternative RNAP sigma factor S (RpoS) is important for the development of stationary-phase-dependent acid tolerance response in Gram-negative bacteria such as *Salmonella* (Álvarez-Ordóñez et al. 2012), while the sigma factor B (σ^B) plays the same role in Gram-positive bacteria such as *L. monocytogenes* (Smith, Liu, and Paoli 2013). Moreover, σ^B regulates the synthesis of various proteins in *L. monocytogenes* in response to acid stress and osmotic stress (Faleiro, Andrew, and Power 2003). Some studies have confirmed the role of sigma factors in the transcription of stress-related genes (Figure 3). Ye et al. (2019) discovered that acid-adaptation (pH 4.5 to 6.0) in *S.* Enteritidis upregulated genes involved in resistance to acid (SEN1564A and *cfa*), heat (*rpoH*, *uspB*, and *htrA*), salt (*proP*, *proV*, and *osmW*), and cold (*cspA*, *cspC*, and *csdA*). As a consequence, acid-adapted *S.* Enteritidis developed cross-protection to heat (50 °C), NaCl (8%), and low temperatures (−20 and 4 °C). *cfa* gene encodes cyclopropane fatty acid (CFA) synthesis, which participates in major phenotypical changes in foodborne pathogens. The formation of CFAs in the cell membrane is a major factor that protects foodborne pathogens form acid shock by altering cell membrane composition. It has been demonstrated that RpoS regulates the expression of *cfa* in *S.* Typhimurium mainly during stationary phase (Sarjit et al. 2019). SEN1564A gene, which is also regulated by RpoS in *Salmonella*, encodes the acid shock protein SEN1564A. This protein can prevent or repair damages induced by acid stress, thus conferring acid tolerance to foodborne pathogens (He et al. 2018). *rpoH* is the gene that encodes the RNAP sigma factor H (RpoH), which may also be called σ^{32}. RpoH is an important regulator of the heat resistance response in foodborne pathogens and regulates the expression of heat shock proteins in foodborne pathogens upon binding to RNAP (Narberhaus and Balsiger 2003). *uspB* is the gene encoding the universal stress protein B (UspB) and it is regulated by RpoS. This protein not only participates in the stress resistance response to heat, but also against ethanol,

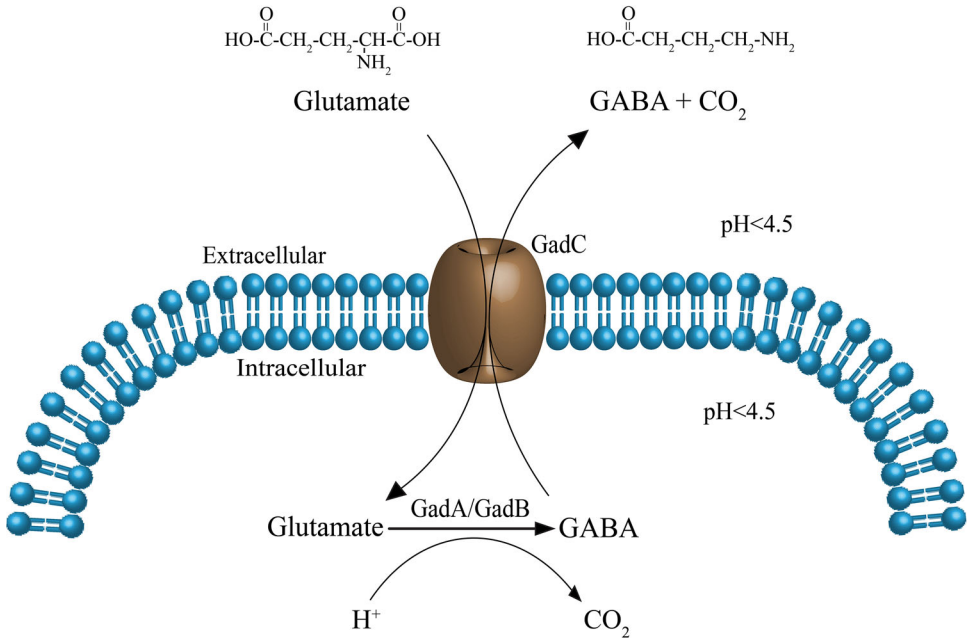

Figure 4. The glutamate decarboxylase (GAD) system in foodborne pathogens as a mechanism of cross-protection response.

osmotic, and oxidative stresses. UspB is known to be an integral membrane protein and together with universal stress protein A (UspA), plays an important role in the alteration of membrane composition under stress conditions (Vollmer and Bark 2018). The stress protein High Temperature Requirement A (HtrA), which is encoded by the *htrA* gene, is essential for protecting bacteria at high temperature. Moreover, *htrA* is regulated by the alternative sigma factor RpoE (Wambui et al. 2020). As a protease and chaperone, HtrA is involved in the quality control of protein synthesis, which is important under stress conditions (Zarzecka et al. 2020). The genes *proP*, *proV*, and *osmW* encode the osmoprotectant transporters ProP, ProV, and OsmW, respectively. These proteins are part of osmoprotectant transport systems that protect foodborne pathogens from osmotic and desiccation stress (Finn et al. 2013; Abdelhamid and Yousef 2020). *proP*, *proV*, and *osmW* are regulated by the alternative RNAP sigma factor E (RpoE) (Finn et al. 2013). *cspA*, and *cspC* genes encode the cold shock proteins (CSPs) CspA and CspC, respectively. CspA and CspC also work as serine proteases. *csdA* encodes the RNA helicase CsdA that facilitates transcription and transalation during cold shock (Ray et al. 2020). *cspC* gene has been found to be regulated by σ^B in *E. coli* (Yamanaka, Fang, and Inouye 1998), though other CSPs may also be regulated by sigma factors in other foodborne pathogens. On the other hand, Kim et al. (2016) also found that low temperature of 4 °C enhanced the survival of non-O157:H7 STEC and STEC O157:H7 to acid conditions in pineapple juice (pH 3.8). A real-time quantitative Polymerase Chain Reaction (qPCR) assay showed that *rpoS*, *gadA*, and *adiA* genes were upregulated; therefore, RpoS, which was probably upregulated following exposure to cold and acid, might be involved in the regulation of *gadA* and *adiA* genes. Although the discovery of sigma factors was over a half century ago and enormous progress has been made in understanding their role in the cell (Feklístov et al. 2014), there is still a huge gap of knowledge about the role of sigma factors in cross-protection of foodborne pathogens. Given the great diversity of bacterial strains and stress conditions, sigma factors may trigger or assist in many different ways on other molecular mechanisms of cross-protection of foodborne pathogens. However, this remains to be further explored.

Glutamate decarboxylase (GAD) system

The glutamate decarboxylase (GAD) system is an important system for acid resistance in many Gram-positive and Gram-negative foodborne pathogens (Arcari et al. 2020). When a bacterial cell is exposed to extracellular low pH, an extracellular molecule of glutamate is imported to the cell by an antiporter. Then the GAD system catalyzes the extracellular glutamate to one molecule of γ-aminobutyrate (GABA), which is then expelled from the cell by an antiporter. This process consumes one intracellular proton (Figure 4). Thus, the GAD system reduces the proton concentration sustaining pH homeostasis in the cell (Alonso-Hernando, Alonso-Calleja, and Capita 2009; Liu et al. 2015). The GAD enzyme, which is a pyridoxal 5′-phosphate (PLP)-dependent enzyme, works at an optimum acidic pH (3.8 – 4.6). The enzyme (GadB) is localized in the cytoplasm at neutral pH. But at low pH, it is mobilized to the membrane where is able to work with the glutamate/GABA antiporters (Feehily and Karatzas 2013). Previous studies have shown the role of GAD system in acid-adaptation and cross-protection. Wemekamp-Kamphuis et al. (2004) found that GAD system was important for the mechanism of acid-adaptation (pH 2.5) of *L. monocytogenes* and subsequent cross-protection in response to high hydrostatic pressure (up to 400 MPa) and freezing (−20 °C). Szendy et al. (2019) reported that *L. monocytogenes* strains used the GAD system to tolerate the exposure of lethal levels of nisin; thus, other

foodborne pathogens may also display similar phenomenon. This suggests that reducing the level of free glutamate in acid foods containing nisin may prevent the growth of resistant GAD$^+$ *L. monocytogenes* strains. Boura, Brensone, and Karatzas (2020) found that the upregulation of GAD genes was responsible for the oxidative stress resistance of *L. monocytogenes* after H_2O_2 exposure. As the GAD system is used by foodborne pathogens to survive acid stress and it is most likely to be induced by exposure of low pH, it is interesting to see that the GAD system is also involved in the resistance response to other stresses. Therefore, the GAD system may be a mechanism for cross-protection involving acid and other stresses. Moreover, it is suggested that these research outcomes should be considered in the design and application of food hurdle technologies to eliminate foodborne pathogens. The great variability in the usage of this mechanism between species and strains indicates that more work needs to be done to have a better understanding of its role in stress resistance (Feehily and Karatzas 2013). As discussed in section 3.1, sigma factors may also be involved in the other specific molecular mechanisms. It has been reported that the expression of *gad* genes (*gadB*, *gadC*, *gadD*, and *gadE*) in *L. monocytogenes* is regulated by σ^B, while *gadA* plays a minor role in acid adaptation (Wemekamp-Kamphuis et al. 2004). Thus, it can be assumed that in different bacterial strains, under different conditions, different sigma factors may also regulate the expression of *gad* genes.

Protection or repair of molecules

Under acid stress, specific proteins in foodborne pathogens are usually induced to protect or repair macromolecules such as deoxyribonucleic acid (DNA) and proteins (Guan and Liu 2020; Liu et al. 2015). Such proteins are usually classified in groups that work in specialized systems involved in stress resistance and cross-protection such as acid shock proteins (Álvarez-Ordóñez et al. 2012), acid shock proteins (Kragh et al. 2020), osmoprotectant transporter proteins (Ray et al. 2020), and so on. Some chaperones have been considered as important stress resistance factors during transport, folding, and degradation of proteins (Guan and Liu 2020). Chaperones are proteins that assist other proteins to fold during synthesis, refold after partial denaturation, and translocate to their cellular spot (Macario and Conway de Macario 2007).

The class I stress proteins GroEL and DnaK are indisputable molecular chaperones which are important to the tolerance mechanism to environmental stresses in foodborne pathogens. These adenosine triphosphate (ATP)-dependent proteins participate in cellular processes including protein folding, translocation, and assembly/disassembly of protein complexes in prokaryotes (Gaca and Lemos 2019). They protect newly synthesized or stress-denatured polypeptides from misfolding and aggregation (Susin et al. 2006). GroEL is involved in the folding of approximately 10% of newly synthesized proteins in *E. coli* (Wickner et al. 2017). Previous studies have reported the role of GroEL and DnaK proteins in the cross-protection of foodborne pathogens. Malheiros et al. (2009) reported that GroEL and DnaK could be involved in the mechanism of cross-protection against heat stress in acid-adapted *S.* Typhimurium and *S.* Bredeney. Chen, Chiang, and Chou (2009b) detected GroEL protein in acid-adapted (pH 5.5) *B. cereus* cells which may be involved in the cross-protection to ethanol (20%) and NaCl (20%). But the authors failed to detect DnaK protein. These results opposes the findings of Periago, Abee, et al. (2002) in which pre-exposition to lactic acid (pH 5.0) in *B. cereus* cells induced the production of DnaK and DnaJ but not GroEL, and was involved in the mechanism of cross-protection to heat (50 °C). Similar findings were reported by Periago, Abee, et al. (2002) in *Bacillus weihenstephanensis*.

The OmpR protein is recognized as a member of the two-component regulatory system OmpR-EnvZ involved in osmoregulation and as an important factor in acid and osmotic stress responses. (Jaworska et al. 2018). OmpR is a stationary-phase acid shock protein (Lee and Kim 2017). Additionally, OmpR is also involved in virulence of pathogenic bacteria (Jaworska et al. 2018). A recent study has shown the involvement of OmpR in acid-adaptation and thermal resistance of *S.* Enteritidis. Ritter et al. (2014) found that OmpR was involved in the cross-protection of *S.* Enteritidis to heat (52 and 60 °C) following acid-adaptation (pH 4.5). OmpR was not induced by RpoS —which is responsible for the induction of many stress resistance proteins—, but by exposing stationary-phase cells to pH during acid-adaptation. Chakraborty and Kenney (2018) found that acid-adapted (pH 5.6 buffered with 100 mM MES) *S.* Typhimurium and *E. coli* showed increased amount of outer membrane protein composition, which was OmpR, suggesting this mechanism for the cross-protection between acid and osmotic stress. These studies provide evidence of the function of OmpR in the cross-protection of foodborne pathogens to various stresses.

Alteration of cell membrane

Cell membrane is the first part of the cellular structure that encounters environmental stress. Cell membrane protects cellular activities under acidic conditions in many ways (Guan and Liu 2020). Alteration of membrane lipid composition is an important adaptation mechanism in foodborne pathogens, which protects them from harsh environment conditions such as low temperature, heat, low pH, high pressure, osmosis, and presence of disinfectants (Diakogiannis et al. 2013) (Figure 5). These changes in lipid composition might be promoted by the upregulation of proteins associated with fatty acid metabolism. Organic acid-adaptation is also an important factor for changes in membrane lipid composition, which decreases membrane fluidity and so providing stress resistance to foodborne pathogens (Yuk and Marshall 2004); it has been observed in *E. coli* O157:H7 (Yuk and Marshall 2005). Moreover, sigma factors may also be involved in the alteration of membrane composition in foodborne pathogens. It has been reported that RpoS was involved in the alteration of outer membrane

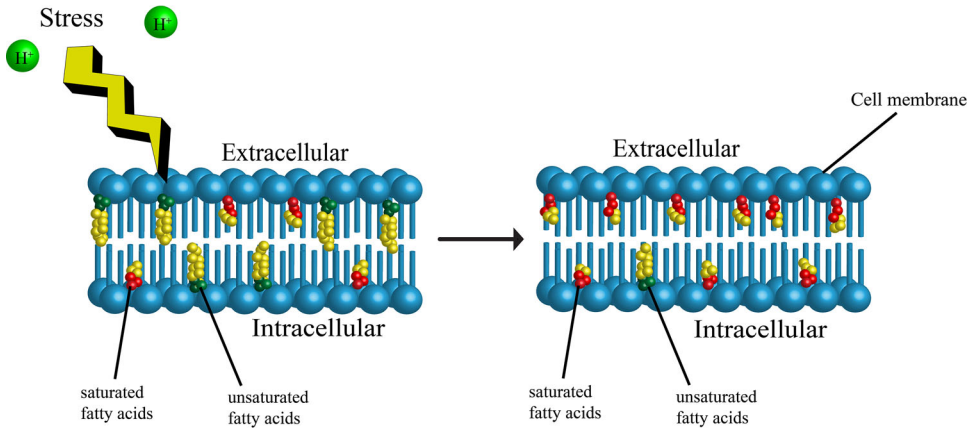

Figure 5. Alteration of cell membrane in foodborne pathogens following acid stress.

composition in Gram-negative bacteria *Flexibacter chinensis* (Rahpeyma and Raheb 2019).

The mechanism of alteration of cell membrane has been widely described in previous studies. Yang et al. (2014) found that lactic acid-adapted *S.* Enteritidis cells presented lower ratio of unsaturated to saturated fatty acids (UFA/SFA) than non-adapted cells, thus possessing less fluid membrane. Decreased membrane fluidity provided heat resistance (54 – 60 °C) to bacterial cells. Álvarez-Ordóñez et al. (2008) also found that in *S.* Typhimurium, low pH conditions (pH 4.5) caused a decreased in UFA/SFA ratio and in the C18:1 relative concentration, and an increase in cyclopropane fatty acids, resulting in decreased membrane fluidity. Thus, acid-adapted cells with low UFA/SFA ratio and low membrane fluidity showed higher heat resistance (45 °C) than non-adapted cells. Similarly, Álvarez-Ordóñez et al. (2009c) found that lower UFA/SFA ratio and higher fatty acid content in acid-adapted (pH 4.5) cells compared with those in non-adapted cells of S. Seftenberg were also linked to cross-protection to heat (63 °C). Hu et al. (2020) found that three proteins associated with fatty acids metabolism were upregulated in *S.* Enteritidis in response to acid stress, namely FabI, FabZ, and AccA. The upregulation of FabI and FabZ was associated with the accumulation of unsaturated fatty acids in the membrane in response to acid stress. Additionally, FadL, which is the outer membrane transporter of long-chain fatty acids, was upregulated. Nicotinamide adenine dinucleotide phosphate (NADPH), which is generated by FabI, promotes the reduction of oxidized glutathione (GSSH) to glutathione (GS-H). GS-H can protect bacteria from acid, oxidative, and osmotic stress. Koga et al. (1999) found that acid-adapted (pH 5.3) *V. parahaemolyticus* showed increased amount of outer membrane protein composition, suggesting this mechanism for the cross-protection to heat, crystal violet, bile, and deoxy cholic acid. Kang et al. (2015) suggested that acid-adaptation in *L. monocytogenes* altered the membrane fatty acid profile, which reduced membrane fluidity. This mechanism conferred cross-protection against antimicrobials nisin and ε-polylysine to *L. monocytogenes* cells. Moreover, Diakogiannis et al. (2013) discovered that different acids had different effects on the total lipid in cell membrane of *L. monocytogenes*. Bacterial cells treated with HCl or acetic acid decreased more the membrane fluidity compared with those treated with benzoic or lactic acid. Interestingly, heat adaptation may also alter membrane lipid composition in foodborne pathogens such as *E. coli* O157:H7 (Yuk and Marshall 2003). The number of studies regarding alteration of membrane composition is bigger compared to other mechanisms. However, these studies are somehow superficial, which means that they fail to go deeper in the understanding of associated genes at the molecular level.

Future trends in the research of cross-protection responses

Among various future trends in the research of cross-protection responses in foodborne pathogens, the most important one would probably be to decipher the exact underlying mechanisms. Though many theories, including the role of stress-related genes in the mechanisms of acid tolerance response of some foodborne pathogens are proposed in the literature, the exact mechanism of cross-protection is still inconclusive. Moreover, it is difficult to generalize resistance mechanisms for all bacteria, because different species and even different strains use different elements as response to acid stress (Guan and Liu 2020). If there is such difficulty in acid tolerance mechanism, one can imagine the difficulty in studying the mechanisms of cross-protection. These mechanisms are systems that may involve the interaction of multiple parts at the molecular level. Therefore, techniques used in molecular biology such as transcriptomics and metabolomics may help to understand the cross-protection mechanisms. These techniques would provide great assistance to proteomics, which has been extensively used to characterize bacterial stress response mechanisms (He et al. 2019). Their combined use would allow an in-depth understanding and elucidate many questions regarding the molecular mechanisms of cross-protection.

The second topic of interest in the future might be the investigation of cross-protection response of foodborne pathogens in food materials. For example, fermented, acidified, or acid foods might provide suitable environments of acid-adaptation for foodborne pathogens. Acid-adapted pathogens in these food matrices would survive to

subsequent treatments or hurdles such as heat, salt, cold, and non-thermal technology (Bucur et al. 2018). Meat products are also prone to be reservoirs of acid-adapted foodborne pathogens. Organic sprays such as lactic, acetic, or citric acid are routinely used in slaughterhouses and meat processing plants in some countries for controlling the proliferation of foodborne pathogens. This practice includes spraying directly to animal carcasses or final products (Burin, Silva, and Nero 2014); thus, potentially inducing acid-adaptation in foodborne pathogens, which may survive to subsequent stresses or multiple stresses.

In the process of cross-protection, some stress response regulators (such as RpoS in Gram-negative bacteria and SigB in Gram-positive bacteria) usually participate in the regulation of virulence level of foodborne pathogens and play a synergistic transcriptional regulation effect. Therefore, these regulators enhance the expression of specific virulence factors and help pathogens enter the host body for survival (Alvarez-Ordóñez et al. 2015). For instance, Werbrouck et al. (2009) showed that *L. monocytogenes* activated SigB under acid stress, which in turn upregulated the expression level of virulence gene *inl*A and significantly increased the ability of bacteria to invade Caco-2 cells. SigB can also regulate the transcription of PrfA, the main virulence regulator of *L. monocytogenes*, and several virulence genes can be regulated by PrfA and SigB, simultaneously (Neuhaus et al. 2013). Moreover, several environmental conditions such as pH value and high temperature can induce the response of RpoS in *Salmonella* and subsequently regulate virulence genes (Burda et al. 2018).

The food safety risk of cross-protection increases even more with the increasing demand for minimally processed food. This trending demand seems to increase, as more and more consumers prefer fresh-like food products with enhanced nutritional quality, characteristics of which are not found in thermally processed foods (Wang, Buchanan, and Tikekar 2019). Thus, current trends have shifted to the study of cross-protection response of foodborne pathogens to non-thermal technologies (Lim and Ha 2021; Liao et al. 2018).

Conclusions

Foodborne pathogens encounter multiple stresses throughout the extensive food chain. Acid stress is among the most common stresses which pathogens might potentially come across. Many foodborne pathogens after exposure to acid stress have managed to develop acid-adaptation and in a worst-case scenario, cross-protection mechanisms to several other stresses. This cross-protection phenomenon could potentially represent serious implications for food safety, since some fermented, acidified, or acid foods which are commonly consumed, could provide auspicious environments to induce the development of acid-adapted cells that are able to survive subsequent treatments such as heat, salt, cold, antibiotic, disinfectant, or non-thermal technology. However, the knowledge gap in this field is still huge, since there are major differences between bacteria strains and stress conditions, and most researches lack an in-depth understanding of the exact mechanisms underlying cross-protection response. Therefore, further studies are required to clarify the exact molecular mechanisms for cross-protection in a variety of acid-adapted bacteria, and to propose customized strategies to ensure food safety.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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