

## Review / Derleme

# Stress responses of *Listeria monocytogenes*

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**Summary:** Bacteria are exposed to stress factors, such as heat, acid, freezing, desiccation and oxidation, in all links of the food chain. *Listeria monocytogenes* has the ability to grow at high salt concentrations, over wide pH and temperature ranges. Because of its ability to tolerate adverse conditions such as low water activity and low temperature, the elimination of *L. monocytogenes* and controlling of foodborne *Listeria* infections are difficult in food processing plants. Understanding the mechanisms of stress tolerance of *L. monocytogenes* may provide new ideas for controlling of listeriosis and the bacteria. In this paper cold, heat, osmotic, acid, alkali and oxidative stress responses of *L. monocytogenes* and the roles of sigma factors are reviewed.

Keywords: *Listeria monocytogenes*, sigma factor, stress.

## *Listeria monocytogenes*'in stres yanıtları

**Özet:** Bakteriler, gıda zincirinin tüm aşamalarında ısı, asit, dondurma, kuruma, oksidasyon gibi stress faktörlerine maruz kalmaktadır. *Listeria monocytogenes* yüksek tuz konsantrasyonlarında, geniş pH ve sıcaklık aralıklarında gelişebilmektedir. Düşük su kapasitesi ve düşük sıcaklık gibi zorlu şartları tolere edebildiği için gıda işletmelerinde yok edilmesi ve enfeksiyonlarının kontrolü zordur. *L. monocytogenes*'in stres tolerans mekanizmalarının anlaşılması, listeriosis ve bakterinin kontrolü için yeni fikirler sunabilir. Bu derlemede *L. monocytogenes*'in soğuk, sıcak, osmotik, asit, alkali, oksidatif stress cevapları ve sigma faktörleri değerlendirilmiştir.

Anahtar kelimeler: *Listeria monocytogenes*, sigma faktörü, stres.

## Introduction

The capacity of *L. monocytogenes* to survive and multiply under a wide range of environmental-stress conditions appears to be critical for foodborne transmission of the pathogen. Accordingly, a number of transcriptional regulators important for stress response and virulence gene expression have been identified in the organism. Harmful factors affecting the growth of microorganisms in a negative way are called as "stress". The reactions occurring in bacteria against stress are the form of long-term adaptation or immediate (shock) response. In many cases immediate and long-term adaptation responses are generated through similar shock proteins. The synthesized proteins may be effective against a single stress factor or multiple stress factors. Moreover resistance mechanisms that are activated by each bacteria against the stress factor may be different or same (61). Also intrinsic resistance to antibiotics is a serious therapeutic problem in the case of many bacterial species (26).

Tasara et al. (55) reported that sensitivity of *L. monocytogenes* EGD-e without cold shock proteins

(Csps) increases against nisin and benzalkonium chloride stress in addition antibiotics containing ampicillin and polymyxin B that support the growth of cells. Furthermore it is stated that the adaptation of *L. monocytogenes* to growth at a low temperature may be affected (27). It is reported that mechanism of resistance formed by *L. monocytogenes* against the low-pH conditions, may be different at each phase of bacterial growth (lag phase, log phase, stationary phase) (39).

## Cold Stress Response

Cold-exposed *L. monocytogenes* cells encounter various molecular difficulties such as the reduction of membrane elasticity, the reduction in protein and enzyme activity, slowing down in nutrient uptake and transport systems, delays in the process of gene expression, change and damage of proteins. The early induction of cold resistant-induced oxidative stress elevates endoplasmic reticulum (ER) stress, which could interfere with keeping phagocytized *L. monocytogenes* within the phagosome or reencapsulating *L. monocytogenes* by autophagy once they escape from the phagosome. Thus, it is postulated that

increased stress, as exists with living conditions at low socioeconomic conditions, can lower host defenses against pathogens because of oxidative and ER stress processes (38).

DNA helicases and Csp's in *L. monocytogenes* are important for the growth of the bacteria. The cold shock proteins are one of the members of family of small and highly conserved chaperones, which play a role in the control of replication, transcription and translation (48). Schmid et al. (51) indicated that *L. monocytogenes* mutants with no *cspA* (*cspL*) and *cspD* genes significantly reduce during cold preservation. It is reported that absence of *lisR*, *lmo1172* and *lmo1060* genes in *L. monocytogenes* reduces the cold adaptation of the bacteria (10). Moreover it is noted that *lhkA*, *yycJ* and *yycF* genes are transcriptionally active in response to cold stress (11, 28). It is indicated that RNA helicases identified in *L. monocytogenes* which are *lmo0866*, *lmo1722* and *lmo1450*, are part of the cold stress response transcriptome (11). Azizoglu and Kathariou (4) showed that the growth of mutants which disrupted *lmo0866* gene decrease at low-temperature.

### Hot Stress Response

Compared with many vegetative microorganisms, the more heat-resistant *L. monocytogenes* can survive during pasteurization especially in dairy products due to living within the cell (49). When bacteria expose to heat stress during heat treatment such as pasteurization, they activate cellular mechanisms to renew the functions of nucleic acids, membranes and organisms, remove degraded proteins, renovate metabolic functions and produce new proteins. Proteins synthesized by organisms repair the damage caused by heat stress. Heat shock response is related to the increase in production of specific proteins (heat shock proteins). Heat shock proteins (Hsps) contain highly conserved chaperones and ATP-bounded proteases. It is stated that the protection of the cells are provided by chaperone proteins like *GroES*, *GroEL* and *DnaK*, by helping protein aggregation at high temperatures (24). *CtsR* inhibitors which control ATP-bounded protease are *ClpP*, *ClpE* and *ClpC*. They decompose damaged or misfolded proteins. *ClpB* makes pelleted proteins active again (25). It is reported that sensitivity to heat stress increases in *L. monocytogenes* cells without *fri* gene (16). Magalhaes et al. (32) suggest that persistent strains may be better adapted to grow under stressful conditions including temperature, NaCl concentration and acidity.

### Osmotic Stress Response

Sugar and sodium salts are used by their dehydration affect as food preservatives for bacterial

cells. They may disrupt many biological functions by increasing the solute concentration in cell. There are some studies about the effects of brine process especially in dairy products on *L. monocytogenes* (29, 50, 52). Osmotic stress adaptation proteins, such as *GbuA*, *AppA*, *Ctc*, *DnaK*, *HtrA* and *OpuC*, are identified in *L. monocytogenes* (1). One of the main osmotic stress adaptation strategies in *L. monocytogenes* is the accumulation of the substances referred as intracellular osmolyte (8). *BetL*, *Gbu* and *OpuC* transport systems involving glycine, betaine and carnitine intake are important in the growth of bacteria under osmotic stress (18). Furthermore *clpC*, *clpP* and *htrA* genes have also been associated with NaCl osmotic stress tolerance (56, 58). *L. monocytogenes* EGD-e strains without *lmo1078* gene are affected negatively under NaCl osmotic stress (12).

The expression of STAT5 transcripts (Signal Transducer and Activator of Transcription) which mediates various biological events such as immune responses, proliferation, differentiation, cell migration, apoptosis, and cell survival, was showed highest expression against *L. monocytogenes* infection, when compared with saline-injected control (6).

### Acid Stress Response

It is known that substances produced by lactic acid bacteria can inhibit a variety of gram negative and gram positive bacteria. There are some studies about the effect of inhibition of starter culture on *L. monocytogenes* in dairy products (37, 60). *L. monocytogenes* faces strong acidic challenge in the gastrointestinal tract during the infection process; therefore survival and adaptation to an acidic environment is essential for systemic infection (47). Bacteria respond in a number of ways against acid stress occurring in such cases such as by stimulating enzymes that repair DNA, by improving the amino acid catabolism and proton pump (proton efflux) and by making changes in the composition of the cell membrane (61). Cellular proton permeability comprises the transformation of the lipid composition with bilayer membrane. It is indicated that the concentration of straight-chain fatty acid increases and the level of branched fatty acids reduces in membranes of *L. monocytogenes* cells which exposed to the acid (21).

It is reported that accelerated electron transfer through increased oxidation-reduction potential may be one of the mechanisms used by bacteria which exposed to acid stress. Dehydrogenases (*GuaB*, *PduQ* and *Lmo0560*), reductases (*YegT*) and respiratory enzymes are trigger the adaptation to acid stress in *L. monocytogenes* cells. This situation includes the active cellular proton flow (42). *L. monocytogenes* provides its

intracellular pH balance by pumping protons from the cytoplasm through FOF1-ATPase proton pump mechanism (36). Glutamate decarboxylase acid resistance system plays an important role in acid stress adaptation of *L. monocytogenes* (57). It is observed that the viability of *L. monocytogenes* cells loses while passing through the artificial gastric juice (about 4 hours) as a result of mutations made in the *gadA*, *gadB*, *gadC* genes which encoded glutamate decarboxylase metabolism (36).

H<sup>+</sup>ATPase also has a role in the initiation of the acid tolerance response. It is shown that the genes which are *atpC* and *atpD* encoded ATPase, are regulated by *prfA* (34). *L. monocytogenes* has a functional ADI system which includes three enzymes, namely ADI, catabolic ornithine carbamoyltransferase (cOTC) and carbamate kinase (CK), encoded respectively by *arcA*, *arcB* and *arcC*. These enzymes catalyse the conversion of arginine into ornithine, NH<sub>3</sub>, CO<sub>2</sub>, and ATP. The ornithine is transferred outside the cell in exchange for arginine by a transporter encoded by *arcD*. The ammonia produced as a byproduct of the system combines with intracellular protons to yield NH<sub>4</sub><sup>+</sup> and this reaction raises the cytoplasmic pH, thereby protecting the cell from the potentially lethal effects of acidic extracellular environments (46). Reduction is observed in lifetime of mutants without *argR* and *arcA* under acid stress conditions at pH 3.5 and pH 4.8. *lmo0038* gene also has function in acid stress adaptation (14).

In a recent study Madeo et al. (31) also provided evidence that thiamine plays a critical role in the acid tolerance mechanisms of *L. monocytogenes*. ThiT is a membrane protein involved in the uptake of thiamine, which is an essential cofactor for several enzymes of central metabolism, particularly the carbohydrate metabolic pathways. The authors demonstrated that thiamine-depleted cultures were significantly more acid sensitive than thiamine-sufficient cultures. Following experiment with transposon mutants, they hypothesized that in the absence of thiamine, cells failed to produce acetoin, a proton-consuming compound derived from pyruvate, which is critical for pH homeostasis (31).

It is stated that *HtrA* (58), *LisRK* are associated with acid stress responses (54). Removal of *lisRK* gene encoding the system of two component signal transduction is resulted in sensitivity of *L. monocytogenes* strains to acid stress in their log phase (36). Bowman et al. (7) investigated the transcriptome response of *L. monocytogenes* to organic acids stress. Exposure to stress of organic acid salt (21mM sodium diacetate at pH 5.0) is associated with gene expression changes such as oxidative stress defense, repair of DNA, modification of cell wall, increased activation of genes of

cofactors and fatty acid biosynthesis, activation of  $\delta^B$ , *PrfA*, *HrcA* and *CtsR* regulons. Proteome analysis applied on *L. monocytogenes* ScottA cells exposed to organic acid salts for the preservation of food, showed an increased production of oxidoreductase and lipoprotein and decreased synthesis of DNA-bounded protein, alpha amylase and *Sec A* (33). Stimulation of acid adaptation also protects *L. monocytogenes* cells against various environmental factors. It is detected that developing tolerance against heat stress, osmotic stress, crystal violet and ethanol increases in cells that are adapted to acid. Furthermore it is reported that virulence of the acid adapted *L. monocytogenes* strains which obtained from the field increases after intraperitoneal injection into mice, compared with non-acid adapted strains (39).

### Alkali Stress Response

During the alkali stress adaptation in microorganisms; there are some changes including stimulation of transporters and enzymes which hold protons, cell surface modifications that support proton keeping besides increasing of acid production. In response to exposing alkali stress, it is discovered that 390 gene copies are synthesized gradually in *L. monocytogenes* cells. The genes that act for alkali stress adaptation also take part in general stress response, soluted transportation and different metabolic systems (22). It is stated that synthesing of *L. monocytogenes* chaperons as *DnaK* and *GroEL* are stimulated in case of alkali stress exposing (22). Gardan et al. (19) stated that the genes that code putative transporter proteins are degenerated in 12 mutants which they defined as sensible to alkali stress. Shen et al. (53) demonstrate that temperature plays a critical role in the induction of alkali stress adaptation in *L. monocytogenes* under sublethal alkaline conditions. Pre-exposure to pH 9.0 tryptic soy broth supplemented with 0.6 % yeast extract (TSB-YE) at 37°C induced pronounced alkali stress adaptation whereas sublethal alkaline pre-exposure at 4°C failed to induce any alkali stress adaptation. Furthermore, this pattern of alkali stress adaptation in *L. monocytogenes* was not dependent on the length of pre-exposure time, the concentration of sublethal alkali, the types of alkaline agents and the growth phases of cells. In addition, alkali stress adaptation induced at 37°C was completely reversed in pH 7.2 TSB-YE within 2 h at 37°C or within 4 h at 22°C. However, once it was induced at a higher temperature, alkali stress adaptation in *L. monocytogenes* remained stable at 4°C for at least 4 h. Their findings suggest that even though cold temperatures do not induce alkali stress adapted phenotypes, but it can maintain the previously acquired alkali stress adaptation much longer in *L. monocytogenes*. Alkali stress adaptation protein

systems of *L. monocytogenes* are still not known certainly.

### Oxidative Stress Response

Bacteria can expose to atmospheric changes based oxidative stress along with chemical agents like detergents and disinfectants. Reactive oxygen species like superoxide, hydroxyl radicals and hydrogen peroxide can be produced as by-products of metabolism and can be accumulated because of metabolic tampering in consequence of respiration chain reduction or other stress factors (7, 8).

To withstand the exposure to oxidative agents, such as hydrogen peroxide and sodium hypochlorite, cells need to activate protein, membrane and nucleic acid damage repair mechanisms. Bacterial ROS (reactive oxygen species) detoxification systems include superoxide dismutase (Sod), catalase (Kat) and alkyl hydroperoxidase (AhpCF), which have been shown to be important in oxidative stress protection of *L. monocytogenes* (30).

It is stated that the strains without Kat and Sod, indicate increased oxidative stress sensitivity, low virulence and macrophages life and low reproductive phenotype (3, 5). It is reported that dps ferritin is also important in protection of *L. monocytogenes* cells from oxidative stress (16). Rea et al. (45) reported that sensitivity of *L. monocytogenes* mutants with no perR (peroxide regulon repressor) to hydrogen peroxide increases and they exhibit low growth.

### Role of Sigma Factors in Stress Responses of *L. monocytogenes*

Sigma factors are subunits of prokaryotic RNA polymerase responsible for the recognition of particular DNA sequences in promoter sites. The promoter recognition by the polymerase is triggered by conditions affecting the cell homeostasis (35). Sigma factors responsible for the baseline expression of genes during normal conditions are called housekeeping sigma factors, and sigma factors with an affinity to promoters for genes needed to respond to “non-normal” conditions are classified as “alternative sigma factors” (2).

*L. monocytogenes* has a total of 5 annotated sigma factors:  $\delta^A$ ,  $\delta^B$ ,  $\delta^C$ ,  $\delta^H$  and  $\delta^L$  with  $\delta^A$  being the housekeeping sigma factor, while  $\delta^B$ ,  $\delta^C$ ,  $\delta^H$  and  $\delta^L$  are considered alternative sigma factors. While  $\delta^B$  is strongly associated with stress response and virulence, the roles of  $\delta^C$ ,  $\delta^H$  and  $\delta^L$  are not as clearly defined, possibly due to limited phenotypic effects.  $\delta^B$  (encoded by sigB) is the alternative sigma factor with the largest regulon, and a sigB deletion mutant have a deficient stress response rendering it more sensitive to adverse conditions (e.g.

acidic environments, oxidative stress, carbon starvation) (2).

In *L. monocytogenes*, the sigma factor B ( $\delta^B$ ) modulates around 140 genes associated with stress responses to a great number of adverse environmental conditions, such as exposure to acid, low temperatures, high NaCl concentrations, heat and oxidative stresses (35).

Sigma B ( $\delta^B$ ) is a positive regulator of some general and cold stress response genes including *fri*, *oppA*, *opuCA* and *ltrC* (10). It is stated that alternative sigma factors  $\delta^C$ ,  $\delta^H$ ,  $\delta^L$  along with  $\delta^B$  are related to regulate cold adaptation processing of bacteria (10, 44, 59).

*L. monocytogenes* class II heat shock proteins are controlled by  $\delta^B$  (56). Loss of  $\delta^C$  function also increases *L. monocytogenes* sensibility to warm application together with  $\delta^B$  (62). It is stated that *L. monocytogenes* mutants which ejected  $\delta^B$  and  $\delta^L$ , are sensible to NaCl salt stress (40, 44).  $\delta^B$  regulated genes in osmotic stress adaptation are related to general stress responses, transcriptional regulation, cell transportation, preservation modification, protein synthesis and modification besides functions related virulence (43). Positively controlled genes through  $\delta^B$ , which is genetically related to osmotic stress adaptation, include osmolyte transporter genes *opuCA* and *gbuA* together with *clpC* and *hfq* genes (1, 15, 43). General stress response protein *ctc* is very important in NaCl salt stress tolerance of *L. monocytogenes* and *ctc* gene is controlled by  $\delta^B$  dependent promoter (20).  $\delta^B$  and  $\delta^L$  are also functionally related to regulate acid stress adaptation of bacteria (13, 44, 57).  $\delta^B$ , *Gad* and *ADI* are positive regulators of acid stress response system genes.

It is stated that synthesis of *Gad* and *ADI* genes is decreasing in the absence of  $\delta^B$  (46). In mutant strains extracted  $\delta^B$ , it has seen a significant decrease in oxidative stress tolerance (17, 23, 41). In recent studies, it is mentioned that the contribution of  $\delta^B$  to oxidative stress may depend on the type of genotype. Oliver *et al.* (41) stated that the loss of  $\delta^B$  induces oxidative stress sensitivity in the strains in Family I, II and IIIB. In infections caused by *Listeria* strains, *Bsh* gene that contributes to the survival of *L. monocytogenes* in intestinal and hepatic phase and encodes bile salt hydrolase (*Bsh*), also controlled by  $\delta^B$ . In the absence of the gene, bile resistance of the bacterium reduces (34).

### Conclusion

The adaptation of *L. monocytogenes* to stress factors is important because of changing the resistant against some factors like heating, cooling, drying which applied food chain. The stress conditions have clearly showed that *L. monocytogenes* has evolved a number of

survival mechanisms. Researches focus specifically on stress response systems in *L. monocytogenes* and these knowledges have evaluated into improved control strategies. Understanding the factors involved in persistence will support the development of strategies to combat the survival of *L. monocytogenes* in the food processing environment. Besides limiting the opportunities for contamination, appropriate cleaning and sanitation procedures and the elimination of growth niches is a critical point, since these allow *L. monocytogenes* to grow and survive despite cleaning and sanitation. *L. monocytogenes* may be able to adapt to diverse stress conditions during foodborne preservation, processing and transmission technologies. This situation might compose potential health hazard for consumers. It is also thought that adaptation of bacteria to some other stress factor like bacteriocin effects the sensibility to antimicrobials which are used against itself. For this reason stress mechanisms must be investigated to find them out.

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