



Review

Listeria monocytogenes Pathogenesis: The Role of Stress Adaptation

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Abstract: Adaptive stress tolerance responses are the driving force behind the survival ability of *Listeria monocytogenes* in different environmental niches, within foods, and ultimately, the ability to cause human infections. Although the bacterial stress adaptive responses are primarily a necessity for survival in foods and the environment, some aspects of the stress responses are linked to bacterial pathogenesis. Food stress-induced adaptive tolerance responses to acid and osmotic stresses can protect the pathogen against similar stresses in the gastrointestinal tract (GIT) and, thus, directly aid its virulence potential. Moreover, once in the GIT, the reprogramming of gene expression from the stress survival-related genes to virulence-related genes allows *L. monocytogenes* to switch from an avirulent to a virulent state. This transition is controlled by two overlapping and interlinked transcriptional networks for general stress response (regulated by Sigma factor B, (SigB)) and virulence (regulated by the positive regulatory factor A (PrfA)). This review explores the current knowledge on the molecular basis of the connection between stress tolerance responses and the pathogenesis of *L. monocytogenes*. The review gives a detailed background on the currently known mechanisms of pathogenesis and stress adaptation. Furthermore, the paper looks at the current literature and theories on the overlaps and connections between the regulatory networks for SigB and PrfA.

Keywords: *Listeria monocytogenes*; virulence; stress response; Sigma factor B (SigB); positive regulatory factor A (PrfA)



Citation: Sibanda, T.; Buys, E.M. *Listeria monocytogenes* Pathogenesis: The Role of Stress Adaptation. *Microorganisms* **2022**, *10*, 1522. <https://doi.org/10.3390/microorganisms10081522>

Academic Editors: Mónica Oleastro and Ana Botelho

Received: 31 May 2022

Accepted: 19 July 2022

Published: 27 July 2022

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1. Introduction

Listeria monocytogenes is a foodborne pathogen that is the causative agent of the human disease, listeriosis. It is primarily a ubiquitous environmental saprophyte found in many environmental niches such as water, soil, and vegetation [1]. Contaminated, often ready-to-eat (RTE) foods are the main transmission vehicles for human *L. monocytogenes* infections [2–4]. In most individuals, *L. monocytogenes* infections frequently result in mild, self-limiting febrile gastroenteritis [5]. However, in susceptible individuals, such as infants, the elderly, pregnant women and people who are immunocompromised, infections result in invasive listeriosis which has a high fatality rate of 20–30% [5]. As an invasive intracellular pathogen, *L. monocytogenes* depends on an arsenal of adhesion and invasion factors that facilitate its gastrointestinal tract (GIT) colonization and transit through the intestinal barrier [6]. Additionally, other virulence factors such as the cytolysin (listeriolysin O), actin polymerization protein ActA and phospholipases are important for the pathogen's intracellular survival and spread of infection [7–9].

As a foodborne pathogen, *L. monocytogenes* encounters several physical and chemical stresses that impede its growth and survival along the food value chain [10]. In response to stress exposures, foodborne pathogens develop mechanisms to adjust cellular processes to a state that allows them to maintain viability and growth under stressful conditions [11]. The development of stress adaptive responses is a process that results from the sensing of

environmental changes and reprogramming of gene expression towards the synthesis of stress response proteins that aid bacterial survival under harsh conditions [12]. This stress adaptation is the driving force behind the ability of *L. monocytogenes* to colonize and survive in different niches within food processing environments and to survive food processing and preservation hurdles [13].

In addition to bacterial stress adaptation being a necessity for survival in foods and the environment, some aspects of the stress responses are linked to bacterial pathogenesis [14]. Being an orally transmitted pathogen, *L. monocytogenes* must overcome the hostile host-defence systems in the human GIT as a first step to establishing a successful infection [14]. Some of these in vivo stress conditions such as acidic pH, increased osmolarity, and oxidative stress are conditions also encountered by the organism in foods and the environment [15]. Hence, food stress-induced adaptive tolerance responses to acid, osmotic and oxidative stresses can protect the pathogen against similar stresses in the GIT, and thus, directly aid its pathogenicity potential [16]. For some time, it has been known that the general stress response regulator (Sigma factor B, (SigB)) that controls the expression of genes for *L. monocytogenes* environmental stress adaptation, also controls the expression of some virulence factors involved in GIT colonization and pathogen internalization by the intestinal epithelium [17,18]. Besides the overlapping function of SigB, evidence has shown that the relationship between stress responses and virulence are intricately connected through direct and indirect interactions between the stress response regulator and the virulence regulator (positive regulatory factor A, (PrfA)) [19–21]. This review explores the current knowledge on the molecular basis of the connection between stress tolerance responses and the pathogenesis of *L. monocytogenes*. The review gives a detailed background on the currently known mechanisms of *L. monocytogenes* pathogenesis and the mechanisms of stress adaptation. Furthermore, the paper looks at the current theories and models explaining the connections between the stress response and virulence regulatory networks.

2. Overview of *L. monocytogenes* Infection Cycle

Through the ingestion of contaminated food, *L. monocytogenes* enters the GIT, where it can traverse the small intestines and establish a systemic infection that disseminates the pathogen to its main target organs (Figure 1). In most healthy individuals, *L. monocytogenes* infections remain largely extracellular within the intestinal lumen and often manifest with intestinal symptoms, typically as febrile gastroenteritis [6]. However, in susceptible individuals, the organism invades the epithelial barrier and crosses into the underlying lamina propria and mesenteric lymph nodes [22]. The organism is subsequently carried in the blood to the liver and spleen through the portal circulation [23]. In the liver and spleen, *L. monocytogenes* is first taken up by Kupffer cells and splenic dendritic cells as resident phagocytes in the respective organs [24,25]. Initially, the bacterial cells are contained within a membrane-bound vacuole inside the phagocytic cells. The bacteria subsequently lyse the vacuole and replicate within the cytosol of infected phagocytes before spreading into neighboring parenchymal cells [23]. In about 2–3 days following the initial phase of invasion, the bacterial multiplication inside the liver reaches maximum growth [23]. The susceptibility of the liver and spleen as the initial target organs for *L. monocytogenes* colonization and replication is thought to be a result of the fenestrated hepatic and splenic capillaries that permit an easy diffusion of *L. monocytogenes* from the bloodstream [23]. As replication niches, the liver and spleen act as reservoirs for *L. monocytogenes*, thus, enabling a re-seeding of the pathogen into the bloodstream, leading to the infection of additional organs [23]. In addition to establishing a systemic infection, studies in experimentally infected mice have shown that the organism can establish long-term colonization of the cecum and lumen of the colon, thus, creating a reservoir for the faecal spread of the organism back to the environment [26].

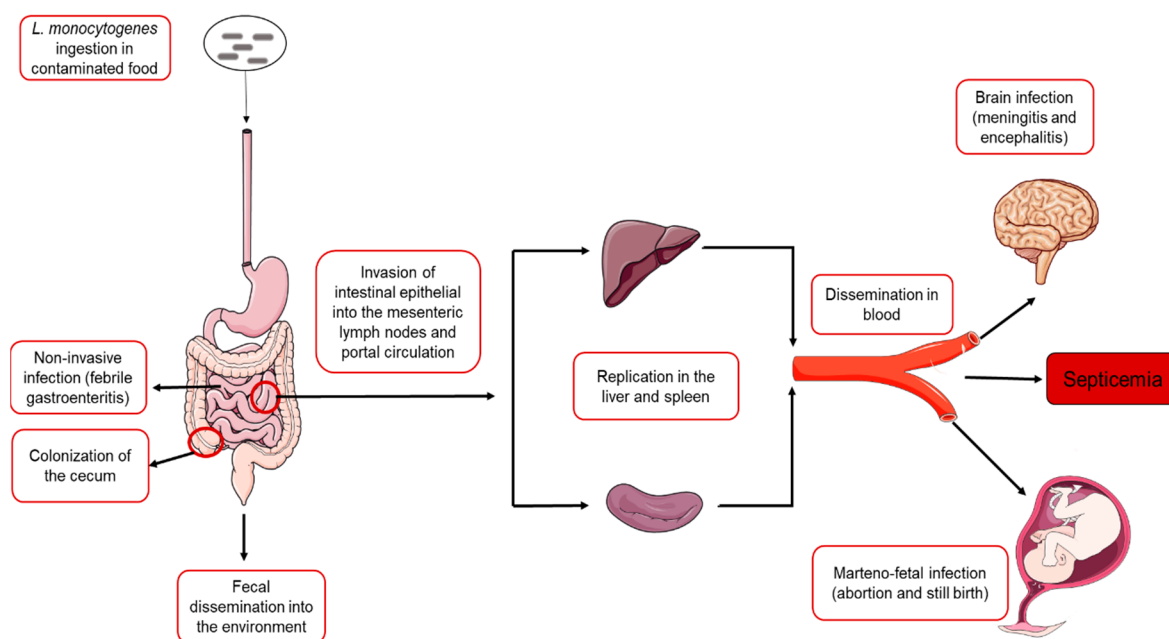


Figure 1. Schematic representation of the infection cycle of *L. monocytogenes* in humans. Following ingestion of contaminated food, the bacteria invade the intestinal barrier into the bloodstream. Through the portal circulation, the organism is transported to the liver and spleen where it multiplies before being disseminated into the bloodstream. The organism subsequently infects the brain and the placenta/fetus in pregnant women. The schematic art pieces were obtained from Servier Medical art (<https://smart.servier.com> (accessed on 1 March 2022)). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

3. Pathogenesis of Invasive *L. monocytogenes* Infections

3.1. *L. monocytogenes* Virulence Factors

L. monocytogenes expresses several surface and soluble proteins that mediate the adhesion to target cells, internalization, intracellular multiplication and dissemination to other host cells [6]. The virulence factors are encoded either as separate loci across the bacterial genome or as clusters on pathogenicity islands [27]. A core of virulence genes (*prfA*, *hly*, *actA*, *plcA*, *mpl*, and *plcB*) encoded on the *Listeria* pathogenicity island 1 (LIPI-1) is conserved in the genomes of all *L. monocytogenes* strains [27]. Additionally, many other virulence factors encoded in separate loci, such as the internalin A/Internalin B (*inlAB*) operon, are also part of the virulence arsenal conserved in all *L. monocytogenes* strains [28]. The characteristics and roles of some of these proteins in the pathogenesis of *L. monocytogenes* are discussed in this section.

Listeria adhesion protein (LAP). LAP is a 104-kDa cell wall protein ubiquitously found in all *Listeria* species [29]. It was first described by Pandiripally et al. [30] as protein p104 which was subsequently found to be an alcohol acetaldehyde dehydrogenase [31]. As an essential enzyme, LAP is produced primarily as a cytosolic protein in all *Listeria* species. However, in pathogenic species, the protein is translocated to the cell surface through the SecA2 secretory system to facilitate the adhesion of pathogenic *Listeria* species to intestinal cells [32,33]. The epithelial receptor for LAP is a constitutively expressed mitochondrial protein, heat shock protein 60 (Hsp60) [29]. In addition to acting as an adhesin, LAP has also been implicated in the translocation of the pathogen across the intestinal epithelium [34].

Fibronectin binding protein (FbpA). Fibronectin binding proteins (Fbp) are cell wall-anchored proteins that are widely distributed in Gram-positive bacteria [35]. Fbps recognize and bind to fibronectin (a component of the human extracellular matrix that plays a role in inter-cellular interaction and adhesion) [36]. The interaction between bacterial Fbps and fibronectin molecules forms a three-component bridge (involving integrins), which facilitates the adhesion between the bacterial and the host cells [35]. The Fbp of

L. monocytogenes (FbpA) was characterized by Dramsi et al. [37]. It is a 570-amino-acid polypeptide that shares a high homology to streptococcal Fbps (PavA of *Streptococcus pneumoniae*, Fbp54 of *S. pyogenes* and FbpA of *S. gordonii*) [37]. However, unlike streptococcal Fbps, the *L. monocytogenes* FbpA is exposed on the surface of the bacterial cell without the signal peptide [37].

Internalin A (InlA). InlA is one of the principal virulence factors of *L. monocytogenes* that was first described by Gaillard et al. [38]. It is an 80 kDa protein that is anchored onto the cell wall peptidoglycan through a C-terminal LPXTG motif [39]. InlA mediates the adhesion and internalization of the pathogen into enterocytes in the first step of invasion of the intestinal barrier [22]. An N-terminal leucine-rich repeat (LRR) domain acts as the recognition and binding site to the EC1 domain of the extracellular portion of E-cadherin [40,41].

Internalin B (InlB). InlB is another adhesion protein that plays a major role in *L. monocytogenes* binding to enterocytes and the subsequent invasion of the intestinal barrier [39]. Unlike InlA, InlB is anchored onto the cell wall through glycine and tryptophan (GW) modules that non-covalently interact with cell wall teichoic acids [42]. The LRR domain acts as the recognition and binding site to Met (a host receptor tyrosine kinase) [22]. *L. monocytogenes* also produces many other LRR proteins classified under the internalin family [43]. However, InlA and InlB have been identified as the principal adhesion proteins that mediate pathogen binding and invasion [44].

Listeriolysin O (LLO). LLO is a 56 kDa pore-forming cytotoxin encoded by the *hly* gene [45,46]. It belongs to the family of cholesterol-dependent cytolysins (CDCs) [46]. It was one of the first *L. monocytogenes* virulence factors identified, based on the ability of virulent strains to cause hemolysis on blood agar [47]. Subsequent experiments identified the hemolysin as a sulfhydryl-activated toxin responsible for the intracellular growth of *L. monocytogenes* in human enterocyte-like Caco-2 cells [48,49]. The role of LLO is the lysis of the internalization vacuole, resulting in the release of the pathogen into the cytosol of host cells [50].

Phospholipases. Two types of phospholipases are required for *L. monocytogenes*. Phosphatidylinositol-specific phospholipase C (PI-PLC) is encoded by the *plcA* gene while phosphatidylcholine phospholipase C (PC-PLC) is encoded by the *plcB* gene [51,52]. PI-PLC plays a complementary role together with LLO in the lysis of the primary and secondary vacuole following pathogen internalization [44]. It catalyzes the cleavage of the membrane phosphatidylinositol into inositol phosphate and diacylglycerol [53]. PC-PLC is a broad-range phospholipase which is particularly required for the lysis of the double-membrane secondary vacuole and the primary vacuole in conditions of LLO deficiency [54]. PC-PLC is synthesized as a 33-kDa precursor that requires cleavage to produce the active 29-kDa enzyme [55]. A zinc-dependent metalloprotease (Mpl) encoded by the *mpl* gene is required for the maturation of PC-PLC [55].

Actin-polymerizing protein ActA. ActA is a surface protein encoded by the *actA* gene [56]. It mediates bacterial motility inside infected host cells through actin polymerization [56]. The protein is anchored on the bacterial cell membrane through its hydrophobic C-terminal domain while the functional N-terminal domain is exposed to the host cell cytoplasm [56]. Within the bacterial cell surface, ActA exhibits an asymmetrical distribution, being more concentrated at one polar end of the cell. The asymmetrical distribution is responsible for the directionality of *L. monocytogenes* motility [57,58]. To facilitate intracellular motility, ActA mediates actin nucleation and filament formation through the recruitment of host vasodilator-stimulated phosphoprotein (VASP) and actin-related proteins-2 and 3 (Arp2/3) complex [59,60].

3.2. Gastrointestinal Tract Colonization and Invasion of Host Cells

Due to its severity and high fatality rates, much of the focus on the pathogenesis of listeriosis is placed on invasive infections. However, evidence shows that non-invasive listerial febrile gastroenteritis outbreaks are very common [61–64]. Non-invasive *L. monocytogenes* infections are typically characterized by enteric symptoms such as vomiting,

non-bloody diarrhea, nausea and fever that occur within a short period (24 h) following the ingestion of contaminated foods [62,65]. The mechanisms underlying the pathogenesis of non-invasive *L. monocytogenes* infections remain unclear [65]. Recently, a few studies have attempted to elucidate the mechanisms of *L. monocytogenes* gastrointestinal tract colonization [26,65]. Based on in vitro and mice models, the actin polymerization protein ActA—which mediates the cell-to-cell spread of the pathogen in invasive listeriosis—has also been implicated in intestinal colonization [26]. Using *actA* gene mutants in orally infected mice, Travier et al. [26] found that ActA can mediate *L. monocytogenes* aggregation both in vitro and in the gut lumen. The postulated mechanism of the ActA-mediated aggregation is based on direct ActA–ActA interactions through the C-terminal regions (which are not involved in polymerization) [26]. In the same study, the researchers found that ActA-dependent aggregation was also responsible for an increased ability to persist within the cecum and colon lumen of mice. Additionally, Halbedel et al. [65] observed a genetic correlation between the *L. monocytogenes* disease outcome (invasive or non-invasive) and the presence or absence of a functional chitinase gene (*chiB*) in which gastroenteritis outbreak isolates possessed a premature stop codon in the *chiB* gene. However, the restoration of chitinase production in a non-invasive isolate could not generate the invasiveness characteristic [65].

The first step in the pathogenesis of invasive listeriosis is the ability of the pathogen to cross the intestinal epithelial barrier. Although the complete mechanisms are still not fully understood, three well-elucidated pathways have thus far been used to explain the process [22]. These three pathways (Figure 2) are the InlA-mediated transcytosis, the LAP-mediated translocation, and the microfold (M-cell)-mediated transcytosis [22].

InlA-mediated transcytosis. The InlA-mediated pathway (Figure 2) is the primary route by which *L. monocytogenes* invades intestinal cells. InlA is a cell wall-anchored protein that mediates the uptake of *L. monocytogenes* into non-phagocytic cells through receptor-mediated endocytosis [66]. InlA promotes pathogen adhesion and the invasion of the intestinal epithelium through an interaction with its receptor, E-cadherin (a component of adherens junctions) [44]. Adherens junctions, tight junctions, and desmosomes are part of the apical junctional complex that provides a paracellular seal between adjacent epithelial cells [22]. The InlA interaction with receptors occurs at sites where E-cadherin is transiently exposed to the intestinal lumen [67,68]. The transient exposure of E-cadherin occurs during cell extrusion and junction remodeling [68]. Furthermore, changes in the shape of goblet cells can also result in the exposure of the E-cadherin component of the cell junctions [67]. Through interaction with the receptor, bacterial cells are taken into the enterocytes by endocytosis and are subsequently then released into the lamina propria by exocytosis [22]. The binding of InlA induces the recruitment of other junctional proteins, α -catenin and β -catenin, as well as actin and p120 catenin, which facilitate E-cadherin clustering at the site of bacterial entry [69]. Subsequently, a post-translational modification of E-cadherin (phosphorylation by the tyrosine kinase, Src and ubiquitination by the ubiquitin-ligase Hakai) induces endocytosis through caveolin or clathrin [22,69]. Ultimately, the InlA/E-cadherin-mediated endocytosis involves components of the host cytoskeleton that facilitate the formation of localized host cell membrane protrusions that force the formation of endocytic vesicles around the adherent bacteria cell [44]. It is now known that host cytoskeletal proteins involved in actin nucleation such as the Arp2/3 complex and VASP are activated in response to InlA binding to its receptors [39,70].

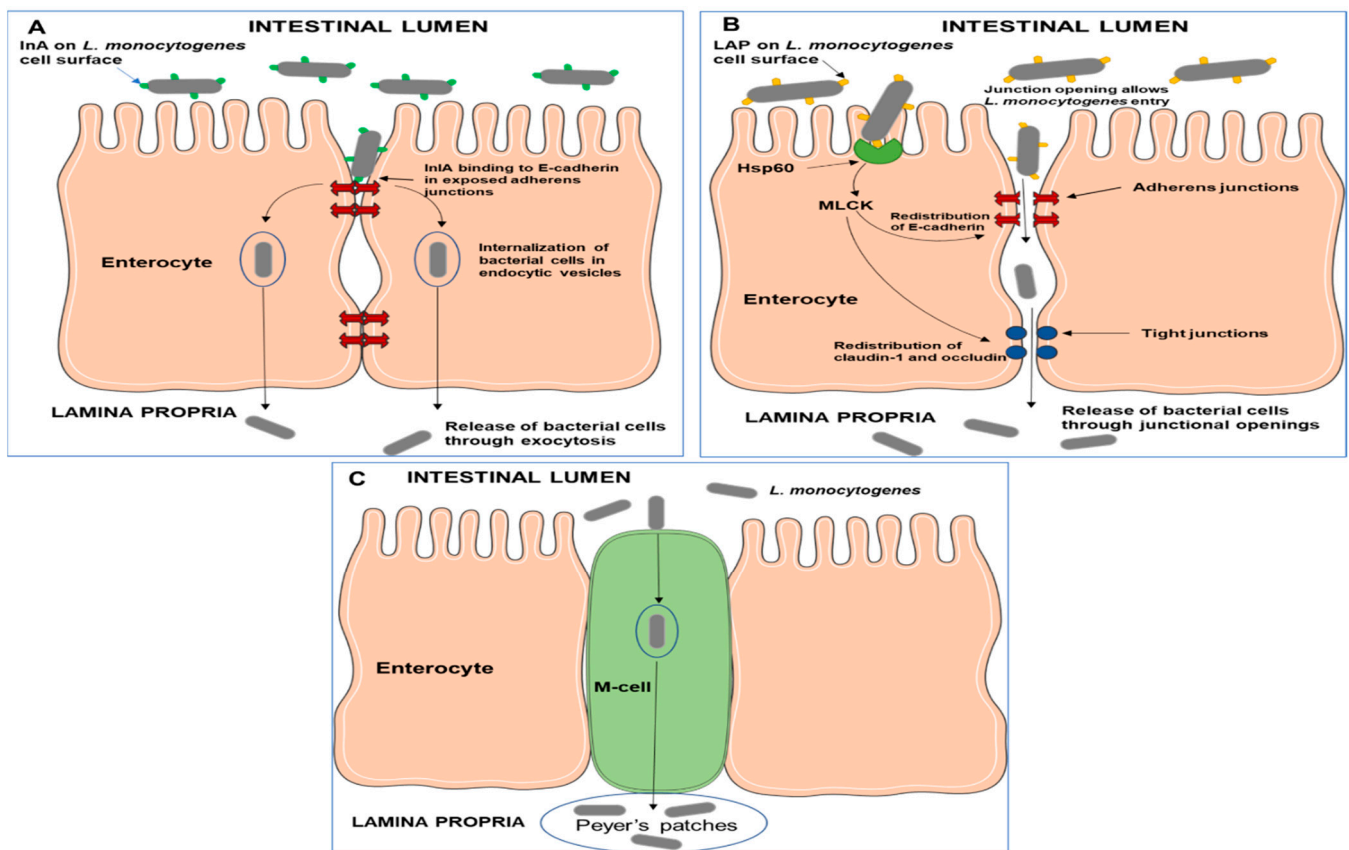


Figure 2. Pathways of the *L. monocytogenes* invasion of the intestinal barrier. In the InIA-mediated transcytosis (A), bacterial cells are taken into the enterocytes by endocytosis through the interaction of InIA and any exposed E-cadherin receptors followed by subsequent exocytosis into the lamina propria. In the LAP-mediated translocation (B), the interaction between the bacterial surface protein LAP and the receptor Hsp60 causes an opening of tight junctions facilitating the movement of bacterial cells into the lamina propria. In the M-cell-mediated pathway (C), bacterial cells are passively taken in by M-cells and released by exocytosis into the lamina propria. The schematic art pieces were obtained from Servier Medical art (<https://smart.servier.com>). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

Unlike InIA, InIB does not play a major role in the invasion of intestinal cells [39]. However, together with InIA, it plays a role in the invasion of other tissues such as the liver, spleen, CNS and placenta [23]. The InIB receptor is the ubiquitous tyrosine kinase Met whose normal ligand is Hepatocyte Growth Factor (HGF) [44]. The binding of InIB to Met results in the autophosphorylation of the cytoplasmic tail of the Met proteins, initiating a reaction cascade that culminates in the localized polymerization of actin and internalization of bacterial cells in the same way as InIA [66].

LAP-mediated translocation. For a long time, the InIA-mediated pathway was established as the main route of *L. monocytogenes* traversal of the intestinal epithelium [67–69]. However, subsequent evidence that strains possessing non-functional InIA could cause infections in orally dosed mice and guinea pigs [71,72] showed that the pathogen can use alternative mechanisms to achieve intestinal invasion [34]. The surface protein, LAP, which was initially identified as an adhesin that facilitates the binding of *L. monocytogenes* to enterocytes, also contributes to the translocation of the pathogen across the intestinal epithelium [34]. The pathway of LAP-mediated invasion (Figure 2) was elucidated by Drolia et al. [34] using a Caco-2 cell line and a mouse model. The researchers showed that LAP induces the intestinal epithelial barrier dysfunction as a mechanism of promoting bacterial translocation. The binding of LAP to its luminal receptor protein Hsp60 acti-

vates myosin light-chain kinase (MLCK) that mediates the opening of the intestinal barrier through the redistribution of junctional proteins, claudin-1, occludin, and E-cadherin [34]. These reactions cause the opening of tight junctions between neighboring enterocytes allowing *L. monocytogenes* translocation [22,34]. Furthermore, the LAP-mediated translocation is thought to be an important precursor event for the InlA-dependent invasion, as it potentially provides pathogen access to E-cadherin in exposed adherens junctions [34].

M-cell mediated transcytosis. The microfold (M) cells are specialized epithelial cells that survey the intestinal mucosa for any antigens as part of the mucosal immune response. They readily take up antigens from the intestinal mucosa and transcytose them across the intestinal epithelium to the lymphoid tissues of the Peyer's patches [73]. This process also serves as a passive route for the transcytosis of pathogens into the basolateral side of the follicle-associated epithelium [74]. While the role of M-cells in the transcytosis of *L. monocytogenes* has been well established, the mechanism of the pathogen interaction with such cells is not fully understood [74]. Evidence from in vitro and orally infected mice models has shown that in the absence of InlA, *L. monocytogenes* rapidly accumulate in the Peyer's patches [75,76]. The prevailing paradigm on the M-cell mediated pathway is that transcytosis occurs across the M cells through a vacuole [22,23]. However, Rey et al. [74] established that in addition to the rapid vacuolar transcytosis, *L. monocytogenes* also escapes to the cytosol of the M-cells by vacuolar rupture. Once in the M-cell cytosol, the pathogen can initiate a direct ActA-based M-cell-to-enterocyte spread [74].

3.3. Intracellular Survival and Dissemination

The ability to cross the intestinal barrier provides the main gate of *L. monocytogenes* entry into the bloodstream. Due to its predilection for the CNS and the placenta in pregnant women, neurolisteriosis, maternofetal infection and septicemia are the main clinical manifestations of invasive listeriosis [77]. The high tropism of *L. monocytogenes* for these tissues is unclear. The possible explanation has been attributed to the presence of E-cadherin and Met, the two receptor proteins for InlA and InlB, respectively [7]. Because of the presence of Met in the human umbilical vein endothelial cells (HUVEC), *L. monocytogenes* can invade the human placenta through an InlB-dependent mechanism [78]. In the CNS, both receptors are expressed at the surface of choroid plexus epithelial cells and Met is additionally expressed at the brain endothelial cells of the blood-cerebrospinal fluid (CSF) and blood-brain barriers. Hence, the invasion of the CNS is facilitated by both InlA and InlB mechanisms [7].

Once internalized into the target cells in a primary vacuole, the next step in the infection cycle is the escape from the primary vacuole into the cell cytosol [79] (Figure 3). This vacuolar escape is mediated by the production of LLO [8,79]. This pore-forming cholesterol-dependent cytotoxin causes the rupture of the vacuole and release of the bacterial cells into the host cell cytosol [80]. In addition to LLO, *L. monocytogenes* also employs phospholipases, such as PI-PLC, that significantly enhance the lysis of the primary vacuole [52]. Following a period of intracellular replication inside infected cells, the production of ActA results in the formation of actin comet tails which facilitate bacterial motility inside the cells as well as the spread to uninfected cells through membrane protrusions [9]. The double membrane of the resulting secondary vacuole is degraded by LLO in collaboration with PC-PLC [9].

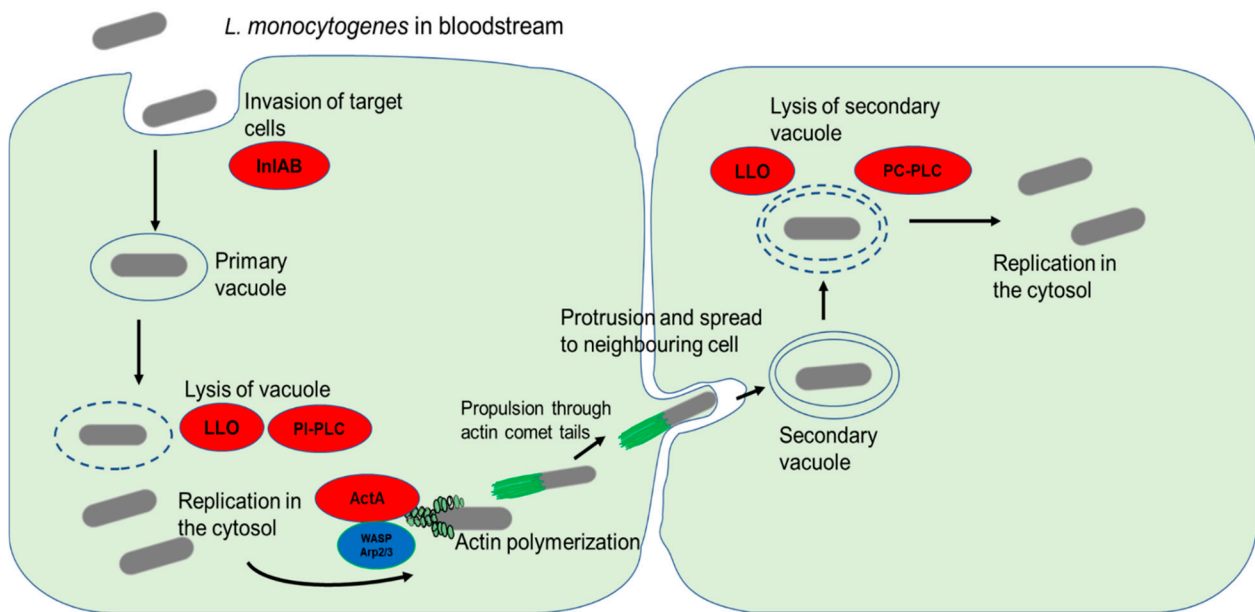


Figure 3. *L. monocytogenes* invasion of target cells and cell-to-cell spread. The bacterial surface internalins InlA and InlB interaction with their respective cell surface receptors result in the internalization of bacterial cells. The primary endocytic vacuole is then lysed through the activity of LLO and PI-PLC. Following a period of replication in the cytosol, the release of ActA stimulates actin polymerization by recruiting host nucleation proteins VASP and Arp2/3 complex. The formation of comet tails propels the bacterial cells and enables them to spread to neighboring cells through membrane protrusions. Lysis of the double membrane of the secondary vacuole by the action of LLO and PC-PLC causes the release of bacterial cells into the cytosol.

3.4. Clinical Outcomes of Invasive *L. monocytogenes* Infections

The clinical outcomes of listeriosis depend on the health status of the infected individual and are often correlated to underlying factors and comorbidities such as cancer, chronic renal, cardiovascular, and liver disease, multi-organ failure, and old age [81–83]. In neuroinfectious listeriosis, the most common symptoms include meningitis, meningoencephalitis, and rhombencephalitis [7]. For maternofetal listeriosis, the main clinical features include amniotic inflammation (amnionitis), preterm labor, stillbirths, and spontaneous abortions. In severe cases, widespread micro-abscesses and granulomatous infantile septica in newborns can occur [84]. Fever, diarrhea, influenza-like symptoms, multi-organ failure, and decompensated comorbidities are the most commonly reported clinical features associated with listerial septicemia [81]. In rare cases, infections can also affect a variety of organs and organ systems [85]. These infections normally involve the cardiovascular system (endocarditis) [86], respiratory tract infections (pleural infections and pneumonia) [87], biliary tract infections (cholecystitis, cholangitis, and biliary cyst infection) [88], and bone and joint infections, especially those involving orthopedic implant devices [89].

4. *L. monocytogenes* Stress Responses and Adaptation

Similar to all living organisms, the ability of *L. monocytogenes* to sense and respond to environmental changes is essential to its survival. Environmental conditions such as osmotic pressure shifts, temperature shifts, pH extremes, changing redox potential and fluctuating nutrient availability impose stress on microbial cells [10]. At their extremes, stress conditions can cause damage to the cellular structural components and disrupt the homeostatic balance inside microbial cells, resulting in cell death [11]. In many instances, microorganisms are exposed to mild stress levels that only reduce growth without causing loss of viability [90]. Due to the demand for minimally processed foods that preserve the natural freshness and nutritional quality, many foods are processed by the use of mild

processing technologies that apply a combination of many sub-lethal stress treatments [91]. Despite the benefits of such approaches, exposure to sub-lethal stresses can induce the development of adaptive stress tolerance responses that enhance the survival of pathogens when exposed to subsequent lethal stress along the food value chain [15]. Many sub-lethal stress hurdles employed in food preservation have been proven to induce adaptive tolerance to lethal stress treatments in *L. monocytogenes* [92–96]. Exposure to sub-lethal acid at pH 5.0, sub-lethal heat at 46 °C, and sub-lethal H₂O₂ at 100 ppm H₂O₂ induces tolerance to lethal acid at pH 3.5; lethal heat at 63 °C and lethal H₂O₂ at 1000 ppm, respectively [95,97,98]. In addition to homologous adaptive responses, heterologous cross-adaptation between different stress factors also occurs [99]. For example, protection against lethal acid stress in *L. monocytogenes* can be induced by sub-lethal NaCl and heat stress exposures [96–98]. The development of adaptive responses has implications for pathogen survival in foods and, subsequently, in the GIT.

4.1. Adaptation to Stress in Foods and Food Processing Environments

The mechanisms responsible for the development of *L. monocytogenes* adaptive tolerance responses against the common environmental and food-related stresses (acid, osmotic, heat, cold, oxidative stress) have been elucidated [95,100–104]. Upon exposure to stress, *L. monocytogenes* modulates the transcription of stress response genes whose effect is to trigger cellular processes that allow the pathogen to survive and grow in the presence of stress [21]. The specific mechanisms of response to acid, osmotic, heat, cold, and oxidative stresses are briefly described in this section.

4.1.1. Osmotic Stress Adaptation

Osmotic stress results from changes in environmental osmolarity that disrupt the cellular osmotic balance [105]. Changes in environmental osmolarity can result from environmental salinity, desiccation and the use of hyperosmotic solutes in foods [106,107]. Extreme hyperosmotic conditions result in loss of cell turgor and cell death due to plasmolysis [105]. The ability of *L. monocytogenes* to withstand hyperosmotic conditions has been known for a long time [98,108]. In response to hyperosmotic conditions, the organism actively accumulates compatible solutes as a way of counterbalancing the negative effects of outward water movement. Compatible solutes are low-molecular-weight, highly soluble compounds that bear a neutral charge at physiological pH, whose accumulation inside the cells helps in restoring cell turgor, without affecting cytoplasmic function [109]. Although several compounds have been identified as potential osmoprotectants, glycine betaine (*N,N,N*-trimethylglycine) and carnitine (β -hydroxy- γ -*N*-trimethyl aminobutyrate) are the most potent at conferring osmoprotection on *L. monocytogenes* [110]. Notably, both compounds are not synthesized by *L. monocytogenes* but are fairly ubiquitous in foods of both plant and animal origin and, therefore, their intracellular accumulation is achieved by active transport from the environment [109,111].

The osmotic stress response is triggered by changes in osmotic pressure as the main signal [112]. However, the mechanism of signal sensing and transduction has only recently been elucidated [113]. The modulation of osmolyte transport and the expression of genes encoding osmolyte transporters is regulated Cyclic di-AMP (c-di-AMP) [105,113]. Two glycine betaine transporters (Gbu and BetL) and a single carnitine transporter OpuC have been known to respond to osmotic upshifts [109]. Gbu is an ATP-dependent transporter encoded by the *gbu* operon that mediates the uptake of glycine betaine in response to osmotic and cold stress [114]. BetL is a non-ATP-dependent secondary transporter encoded by *betL*, whose uptake of glycine betaine is coupled to Na⁺ symport [115]. Carnitine transport is mediated by the ATP-dependent transporter, OpuC, a product of the *opuC* operon that responds to both osmotic and cold stress [116].

4.1.2. Acid Stress Adaptation

Organic acids constitute one of the most frequently used preservatives in foods. Although there are several antimicrobial targets of acids [117–119], the primary antimicrobial effects result from the protonation of the cytoplasm and disruption of intracellular pH [120]. Two amino acid decarboxylation systems (the glutamate decarboxylase (GAD) and arginine deiminase (ADI)) have been known to protect *L. monocytogenes* against acid stress [102,104].

The GAD system depends on the enzyme glutamate decarboxylase, a product of the *gadD* operon which decarboxylates glutamate to produce γ -amino butyric acid (GABA) while consuming a proton and releasing a bicarbonate anion. The decarboxylation is coupled with an antiporter (GadT) that takes out the produced GABA while taking in glutamate [104]. *L. monocytogenes* produces three glutamate decarboxylase enzymes (GadD1, GadD2, and GadD3) and two antiporters (GadT1 and GadT2) that are encoded as pairs consisting of *gadD1T1* and *gadD2T2* operons in separate parts of the genome [104]. The genes have distinct functions in the acid stress response of *L. monocytogenes*. The expression of *gadD1T1* is required for mild acid (pH 5.1) survival, while the *gadD2T2* expression is needed for severe acid stress (pH 2.8), and therefore, is necessary for the adaptive acid tolerance response (ATR) [121].

The ADI system involves the conversion of arginine to ornithine accompanied by the production of ammonia and carbon dioxide [122]. As part of the system, an arginine-ornithine antiporter (protein ArcD encoded by *arcD*) facilitates the uptake of arginine in exchange for ornithine. Once inside the cell, the deimination of arginine by the enzyme arginine deiminase (encoded by the *arcA*) produces ammonia and citrulline. The latter is then converted to ornithine and carbamoyl phosphate through the enzyme ornithine carbamoyltransferase (encoded by *arcB*). Carbamoyl phosphate is subsequently converted to ammonia and carbon dioxide through the activity of carbamate kinase (encoded by *arcC*) [102]. This reaction reduces internal pH through the conversion of ammonia (NH₃) to ammonium ions (NH₄⁺) [123].

4.1.3. Heat Stress Adaptation

Thermal processing is an established method of food preservation, known for its lethality, especially at elevated temperatures. As a non-spore-former, *L. monocytogenes* is generally susceptible to heat stress, although it has been reported to exhibit thermotolerance upon exposure to heat shock at sublethal temperatures [124,125]. Moreover, heat resistance can be induced by exposure to acid, oxidative, alkali, and chlorine stresses [126,127]. The heat stress response is universal in all prokaryotes and is triggered by temperature up-shifts above the normal growth range. Its main effect is the protection of cellular proteins and enzymes against heat-induced denaturation that affects their physiological functions [101]. The heat shock response of *L. monocytogenes* involves the increased transcription of heat shock genes coding for three classes of heat shock proteins (HSPs) [128]. Of these three classes of HSPs, the expression of Class I and Class III proteins is a direct response to heat stress, while Class II proteins are general stress response proteins under the regulatory control of σ^B [101]. Class I HSPs are chaperones made up of the proteins, dnaK, dnaJ, groES, and groEL encoded in two operons (the *dnaK* and *groEL-groES* operons) [129,130]. Class III HSPs are ATP-dependent proteases (clpP, clpC, clpE, and clpB) involved in the proteolysis of misfolded proteins [13]. Under normal growth temperature, the expression of the Class I HSPs and Class III HSPs genes is prevented by HrcA and CtsR repression, respectively [101,131]. Under conditions of elevated temperatures, de-repression is achieved through the reduced DNA binding of repressors and improved binding of sigma factor A, leading to increased transcription [101].

4.1.4. Cold Stress Adaptation

Although *L. monocytogenes* is typically a mesophile, with an optimum growth temperature of 30–37 °C, the organism has a remarkable ability to multiply under low-temperature conditions [132]. While part of this psychrotrophic growth ability may be intrinsic, a signifi-

cant part of it is induced by exposure to cold conditions [133]. At least three mechanisms are utilized by *L. monocytogenes* in response to cold stress-imposed challenges. These include the adjustment of the fatty acid composition of the cell membranes in order to maintain fluidity, the increased expression of cold shock proteins (CSP), and the accumulation of osmolytes and oligopeptides [103].

Upon exposure to low temperatures, the membrane of mesophilic bacteria changes from an elastic liquid crystalline state to a gel-phase state, resulting in the impairment of nutrient uptake [100]. The low-temperature growth propensity of *L. monocytogenes* is related to its ability to maintain membrane fluidity, which is necessary for nutrient transport [134]. The mechanism of cold stress adaptation involves the adjustment of membrane fluidity through the incorporation of unsaturated anteiso-branched-chain fatty acids (BCFA) [135]. Anteiso-BCFAs have a lower melting point than the analogous iso-BCFAs that account for >95% of the membrane fatty acid composition of *L. monocytogenes* cells growing at 37 °C [136]. A key determinant in the adjustment of membrane fluidity is the enzyme β -ketoacyl-acyl carrier protein synthase III (FabH) which catalyzes the initial condensation reaction between iso- and anteiso-branched α -keto acids and acetyl-coenzyme A [135,137].

CSPs belong to a family of small highly conserved and structurally related proteins that are widely distributed in the prokaryotic kingdom [100]. Within the genomes of *L. monocytogenes*, three families of CSP genes (*CspA*, *CspB*, and *CspD* coding for CpsA, CpsB and CpsD, respectively) have been found [138]. While these proteins are dispensable for growth at 37 °C, they are required for growth at 5–10 °C [139,140]. Using directed mutagenesis, Schmid et al. [139] observed that *CspA* is the main CSP required for low-temperature growth of *L. monocytogenes*. Although the exact functions of CSPs are still to be fully elucidated, the current postulation is that these proteins act as nucleic acid chaperones that bind RNA and DNA, thus, facilitating the control of processes such as replication, transcription, and translation within bacterial cells under cold stress [100]. This is presumably necessary to help the organisms overcome the challenges of DNA and RNA supercoiling, which is associated with low-temperature growth [100], coupled with the role of CSPs are RNA helicases, that bind to ribosomes and facilitate RNA maturation challenges at low temperatures [141]. Four DEAD-box RNA helicase genes have been found in the genome of *L. monocytogenes* [142]. Using knock-out mutants, the helicases were found to be necessary for *L. monocytogenes* cold growth [141,143].

L. monocytogenes cold stress adaptation also involves the accumulation of compatible solutes, glycine betaine, and carnitine, as well as oligopeptides as cryoprotectants [103]. The main osmolyte transporters Gbu, BetL and OpuC induced by osmotic stress are also induced by cold stress [144,145]. The accumulation of oligopeptides in *L. monocytogenes* is mediated by the oligopeptide permease transporter (OppA) encoded by the *opp* operon [146]. The exact roles of the accumulated osmolytes and oligopeptides in the cold stress response are unclear. Some posited roles include acting as cryoprotectants and stabilization of enzymes [103].

4.1.5. Oxidative Stress Adaptation

Oxidative stress results from the production and accumulation of reactive oxygen species (ROS) such as superoxide anion, hydrogen peroxide, hydroxyl radicals, peroxy radicals, and singlet oxygen that cause damage to cellular molecules such as DNA, lipids, and proteins [147]. As a facultative anaerobe, *L. monocytogenes* is oxidative stress-tolerant. Catalase and superoxide dismutase encoded by the *kat* and *sod* genes, respectively, are the primary antioxidant enzymes produced by *L. monocytogenes* [148,149]. The two enzymes detoxify the superoxide anion and hydrogen peroxide generated by aerobic metabolism [150]. In addition to the detoxifying enzymes, *L. monocytogenes* possesses a metal-dependent peroxide sensor, PerR (peroxide repressor), that regulates the expression of peroxidase genes and genes for metal homeostasis [151]. The PerR regulon includes *kat*, *fur* (iron homeostasis regulator), *hemA* (haem biosynthesis), *fri* (iron-binding protein) and *forA* (iron efflux pump) [151,152].

4.2. Adaptation to Stress in the GIT

The successful colonization and subsequent GIT invasion by *L. monocytogenes* rely on the ability of the pathogen to overcome the harsh conditions associated with the innate defences of the GIT. The first physical stress encountered by *L. monocytogenes* in the GIT is the low pH of the stomach that the pathogen must deal with as it transits to the small intestines [153]. The critical role of acid stress adaptation in *L. monocytogenes* pathogenesis has been demonstrated through in vitro infection models of enterocyte-like cells and mice models [154,155]. The survival of stomach acidity is attributable to the expression of the GAD system [104]. The *gadD2T2* operon, which is responsible for the ATR of *L. monocytogenes* induced by environmental acid stress exposure, is required for the survival in gastric fluid [104,121].

Once *L. monocytogenes* passes through the low pH of the stomach, it is faced with high osmotic stress and bile stress in the lumen of the small intestines [156]. The resistance to osmotic stress in the GIT has been attributed to the activation of the carnitine transporter *opuC* [116,140]. *L. monocytogenes* mutants with *opuC* gene deletions have been shown to exhibit limited pathogenicity in animal infection models, while the deletion of glycine betaine transporter genes *gbu* and *betL* do not seem to affect virulence [116,140]. The importance of carnitine as the preferred osmolyte in the GIT survival of *L. monocytogenes* is probably linked to its relative abundance in mammalian tissues [140]. Bile stress tolerance is a critical factor in *L. monocytogenes* GIT survival and colonization. The pathogen produces a bile salt hydrolase (BSH) enzyme (encoded by *bsh*) that catalyzes the hydrolysis of the amide bond between the bile acids (cholic acid and chenodeoxycholic acid) and the amino acid conjugates [157]. The enzymatic hydrolysis is complemented by an increased expression of the transporter protein BileE (a product of the *bilE* gene) which is responsible for bile exclusion [158].

5. Crosslink between Stress Responses and Virulence

5.1. Regulation of *L. monocytogenes* Stress Response

In *L. monocytogenes*, the general stress response alternative sigma factor B (SigB) modulates a reprogramming of gene expression that facilitates the survival and protection against harsh environmental conditions [12]. Since it was first described in *L. monocytogenes* three decades ago [159], several roles of SigB have been identified [160–163]. The identified regulon of this general stress response regulator encompasses more than 200 genes that are involved in environmental stress survival, metabolism, and virulence [20,164]. As a general stress response regulator, SigB mediates survival under a broad range of lethal stresses along the food value chain. Transcriptomic and mutagenesis experiments have shown that responses to the common environmental and food stress factors (acid, osmotic, heat, cold, oxidative stress and nutrient stress) are sigB-dependent [20,159,165–167]. Although SigB is the central transcriptional regulator of stress survival genes in *L. monocytogenes*, some alternative transcriptional regulators are also utilized in response to specific stress factors. For instance, the expression of Class I and Class III *hsp* genes relies on HrcA and CtsR proteins as negative regulators [101], while the peroxide repressor PerR regulates the expression of oxidative stress response genes [151].

In addition to regulating stress responses in the environment, SigB also modulates gene expression in response to stress conditions encountered along the oral infection route. *sigB* deletion mutants exhibit limited pathogenicity in orally infected model animals [168]. The SigB modulation of the *gadD2T2* operon, *opuC*, *bsh* and *bilE* gene expression is critical to the survival of stomach acidity, intestinal osmotic and bile stresses, respectively, as a prerequisite for a successful intestinal invasion [116,121,157,158]. Besides its role in stress survival and adaptation, evidence shows that SigB also plays a critical role in the invasion of the intestinal barrier and initiation of infection [12,21]. Thus, the general stress response regulator facilitates a smooth transition from the environmental saprophytic life cycle to the pathogenic life cycle inside host cells.

Molecular Mechanisms of SigB-Dependent Regulation

The SigB protein is encoded by the *sigB* gene as part of an operon that includes seven other genes referred to as the regulation of sigma B (*rsb*) genes (*rsbR*, *rsbS*, *rsbT*, *rsbU*, *rsbV*, *rsbW*, and *rsbX*) coding for Rsb proteins [169]. The Rsb proteins are responsible for the detection of environmental stress signals and the regulatory cascade that controls the activity of SigB. The sensing and transduction of environmental signals is mediated by a 1.8 MDa supra-macromolecular stressosome consisting of a complex of RsbR-RsbS-RsbT proteins [12,170]. Although the exact mechanisms of stress sensing are not clearly understood, the current model is based on phosphorylation events by the sensor kinase RsbT and its subsequent release from the stressosome complex (Figure 4). RsbT subsequently activates RsbU, converting to an active phosphatase. Through its dephosphorylation activity, RsbU in turn activates RsbV [12,171]. In exponentially growing cells, the SigB protein exists as an inactive form bound to the anti-SigB protein, RsbW [169]. The activation of SigB is achieved by a partner-switching mechanism in which the release of RsbW is mediated by the binding of the dephosphorylated form of the anti-SigB protein, RsbV (Figure 4) [169].

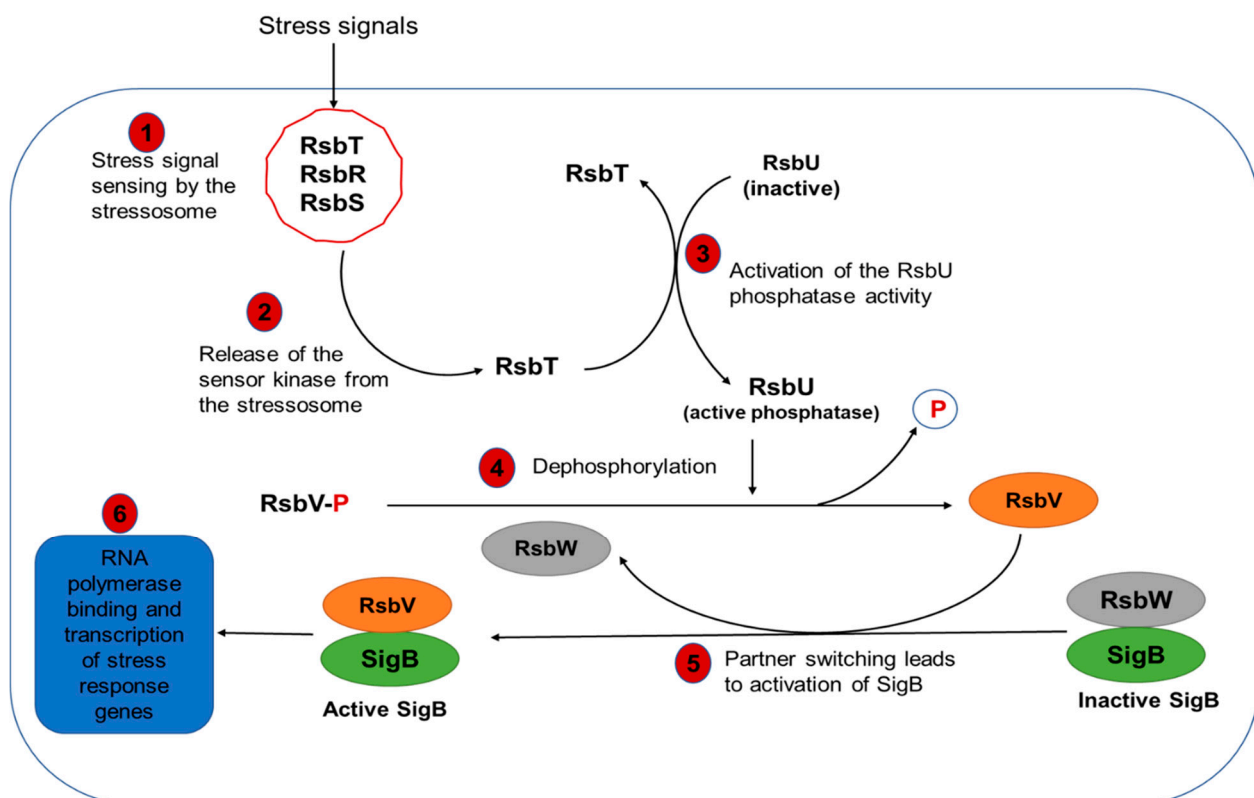


Figure 4. Mechanism of Rsb-mediated regulation of SigB expression and activity in *L. monocytogenes*.

5.2. Regulation of *L. monocytogenes* Virulence

The transition of *L. monocytogenes* from an environmental saprophyte to an intracellular pathogen is facilitated by changes in gene expression patterns from environmental survival-related genes to intracellular survival-related genes. Central to the transition is the role of the protein PrfA, encoded by the *prfA* gene [172]. PrfA is a 27 kDa member of the cyclic AMP receptor protein (Crp)/fumarate nitrate reductase regulator (Fnr) family of bacterial transcription factors [28,173]. The Crp/Fnr transcriptional activators are symmetrical homodimers consisting of an N-terminal cAMP binding domain and C-terminal DNA binding domain [28]. Its regulon includes a block of virulence genes (*hly*, *actA*, *plcA*, *mpl*, and *plcB*) encoded by the *Listeria* pathogenicity island 1 (LIPI-1) and the *inlAB* operon on a separate chromosomal locus [172,174,175]. Apart from the invasion proteins, *inlA* and *inlB*, the role of PrfA in *L. monocytogenes* pathogenesis is largely on the expression of virulence

factors associated with the intracellular stage of the infection as well as the cell-to-cell spread [19,176]. Hence, the transcriptional regulator is activated once the pathogen is in the cytosol of host cells, switching the bacterial cells from the avirulent to the virulent state [176]. The signals and mechanisms that trigger *prfA* expression in the host cytosol have only become clearer in the last decade [177–179]. Branched chain amino acids (BCAA) and phosphorylated hexoses have been identified as the metabolic signals inside host cells [180,181]. An exception to the need for intracellular activation has been observed with *L. monocytogenes* mutants that constitutively express the *prfA* gene (*prfA** mutants) [182,183]. Such *prfA** mutants exhibit a high virulence in animal infection models. However, their environmental stress survival ability is poor [176]. PrfA activates transcription by binding to the PrfA box, a 14-bp A/T-rich palindromic nucleotide sequence located ~40 bp upstream of the transcriptional start sites of genes under its control [21].

5.3. Regulatory Intersection between Stress Response and Virulence

A plethora of evidence has shown that responses to stress in *L. monocytogenes* influence pathogenesis [150,154,184–186]. In most reports, the relationship between stress response and pathogenesis is attributed to adaptive tolerance responses that enable the pathogen to survive host innate defences in the GIT [15,16]. Along with the adaptive stress tolerance, the relationship can also be attributable to overlaps and direct interaction between the regulatory networks of stress and virulence [12,21]. Some of the currently understood mechanisms behind the interplay between the stress and virulence regulatory networks are described in this section. An illustration of the overlap and interactions between transcriptional regulators of stress and virulence is depicted in Figure 5.

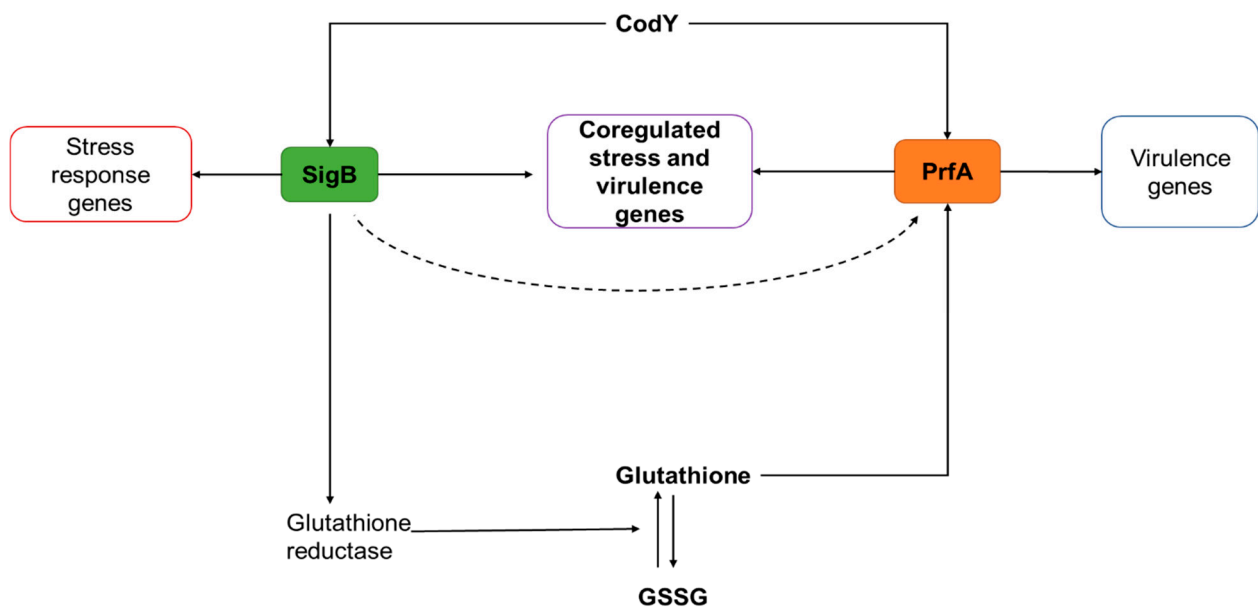


Figure 5. An illustration of the overlap and interactions between SigB and PrfA in *L. monocytogenes*. Solid arrows indicate positive regulation. The dotted arrow indicates negative regulation.

Coregulation of the *inlA/B* operon, *actA* and *bsh*: The dispensability of SigB in the pathogenesis of *L. monocytogenes* is a fact that has been established for a long time [18,168]. The initial evidence for the role of SigB in *L. monocytogenes* pathogenesis was based on observations that *sigB* deletion mutants are avirulent on oral infection but are fully virulent when injected intravenously [168]. Subsequent elucidation of the role of SigB established that in addition to its stress regulon, this transcriptional regulator extends to the control of virulence genes *inlA*, *inlB*, and *actA* (Table 1) [58,187]. The overlapping regulatory controls of SigB and PrfA on the *inlAB* operon provide the connection between the stress response and virulence of the pathogen [156]. The biological significance of this coregulation of the

inlAB operon has been explained in terms of the need to facilitate a transition from GIT survival to the invasion of the intestinal barrier, in which SigB is necessary for initiating infection in the intestinal phase before yielding the regulatory function to PrfA in the intracellular stages of infection [156]. Moreover, PrfA also extends its regulatory network to some stress response genes involved in the GIT survival phase (Table 1), such as the *bsh* gene [184,188]. Guariglia-Oropeza et al. [184] suggested a model where SigB-dependent gene expression plays a role in the survival of acid and osmotic stress exposures in the early stages of GIT infection before the subsequent induction of PrfA by the exposure to bile. This intestinal expression of PrfA regulon potentially primes *L. monocytogenes* for the subsequent intracellular stage of infection. While ActA is primarily a virulence factor necessary for the intracellular stage of *L. monocytogenes* infection, it is also produced in the extracellular environment, where it mediates aggregation and biofilm formation [26,58]. Within the intestinal lumen, *actA* expression is under the dual regulation of both SigB and PrfA and is necessary for GIT colonization [26,189].

Table 1. Stress response proteins and virulence factors expressed by *L. monocytogenes* at different stages of the infection cycle.

Stage of Infection Cycle	Stress Response Proteins/Virulence Factor	Function	Transcriptional Regulator	References
Intestinal phase	GadD2T2	Glutamate decarboxylase for survival of stomach acidity	SigB	[104]
	OpuC	Carnitine transporter for osmotic stress survival	SigB	[116]
	Bsh	Bile salt hydrolase for bile stress survival	SigB and PrfA	[157,184]
	BilE	Bile exclusion system for bile stress survival	SigB and PrfA	[158]
	InlA	Adhesion and invasion of enterocytes	SigB and PrfA	[39,168]
	InlB	Adhesion and invasion of enterocytes	SigB and PrfA	[39]
Intracellular phase	ActA	Bacterial aggregation and intestinal colonization	SigB and PrfA	[26,189]
	LLO	Primary vacuole lysis	PrfA	[46]
	PI-PLC	Primary vacuole lysis	PrfA	[53]
	PC-PLC	Secondary vacuole lysis	PrfA	[54]
	ActA	Intracellular motility and cell-to-cell spread	PrfA	[56,190]

SigB downregulation of *prfA* expression and maintenance of basal levels: A growing body of evidence indicates that the interactions between SigB and PrfA extend beyond the coregulation of the *inlAB* operon (Figure 5) [19,191]. Three transcriptional promoters (*prfAP1*, *prfAP2* and *prfAP3*) are utilized in the control of *prfA* expression in *L. monocytogenes*. Of these, *prfAP1* and *prfAP2* are intragenic promoters located upstream of the *prfA* gene on the LPI-1 that are activated by the vegetative sigma factor A (for *prfAP1*) and both sigma factor A and SigB (for *prfAP2*) [192]. However, the biological significance of SigB regulation of *prfA* expression has not been easy to establish [19]. The current hypothesis is that SigB regulation through the *prfAP2* promoter may facilitate the downregulation of *prfA* transcription [19,28]. The repression is postulated to keep a basal level of PrfA that allows for a sensitive and rapid shift from the avirulent state to a virulent state once inside host cells [28]. Thus far, the main mechanism for the upregulation of *prfA* transcription inside host cells appears to be the positive autoregulatory feedback loop through the *prfAP3* promoter [19]. The signal that triggers the upregulation of *prfA* transcription inside host cells remains unclear. One established observation is the role of temperature in the *prfA* expression [193,194]. In *L. monocytogenes*, a thermosensor located in the 5'-untranslated region (5'-UTR) of the *prfA* mRNA transcript allows for the translation of transcript at 37 °C, while preventing translation at temperatures <30 °C [195].

The metabolic regulator CodY as a link between SigB and PrfA networks: CodY is a Gram-positive bacterial metabolic regulator that responds to intracellular Guanosine-5'-triphosphate (GTP) concentration as an indicator of nutrient stress [196]. Under conditions of nutrient availability, CodY represses *sigB* expression, while activating the stress response regulator under conditions of nutrient stress [179]. Apart from GTP as the nutrient stress signal, CodY also responds to the cellular concentrations of branched chain amino acids (BCAA) [180]. Due to the low BCAA concentrations in host cells during infection, CodY plays a critical role in the biosynthesis of BCAAs through the upregulation of the

ilv (isoleucine, leucine and valine (ILV)) operon [180]. Simultaneously, CodY results in an increased expression of virulence gene expression through a direct upregulation of *prfA*, while also causing an increased *sigB* expression [179]. Thus, the metabolic regulator acts as a link between *L. monocytogenes* metabolism, stress response, and pathogenesis (Figure 5) [178,197].

Glutathione allosteric activation of PrfA as an indirect link between SigB and PrfA networks: Similar to other Crp/Fnr family proteins, PrfA requires a co-factor to improve its DNA binding at promoter sequences [178]. In recent years, the tripeptide glutathione (GSH) has been identified as a post-translational activator of PrfA through allosteric mechanisms [198,199]. In addition to the direct role of SigB in the transcription of *prfA*, the stress response regulator also plays some indirect roles in stimulating *prfA* expression. Through the activity of the enzyme glutathione synthase (encoded by the *gshF* gene), *L. monocytogenes* can endogenously synthesize glutathione [200]. However, due to its antioxidant action, GSH is oxidized to GSSG. To maintain a healthy oxidative state, *L. monocytogenes* produces the SigB-regulated glutathione reductase (encoded by *lmo1433*) to modulate the GSH/GSSG ratio [17]. Thus, SigB contributes indirectly to PrfA activity by maintaining high levels of GSH reductase [12].

Along with the activation of *prfA*, there is also evidence to suggest that some stress response proteins of *L. monocytogenes* are involved in the post-transcriptional modification of some virulence factors [185,201]. For instance, Eshwar et al. [185] showed that *cspABD* deletion mutants could not produce the actin polymerization protein ActA, while Schärer et al. [201] made a similar observation with LLO production. Based on their observation, Eshwar et al. [185] hypothesized that the Csp proteins could be linked to the regulation of virulence gene expression at both transcriptional and post-transcriptional levels in *L. monocytogenes*.

6. Strain and Lineage Variability in Stress Response and Virulence

L. monocytogenes exhibits great heterogeneity within the species. The species is divided into four evolutionary lineages (designated lineages I, II, III, and IV), and 13 serotypes [202,203]. Additionally, using multilocus sequence typing (MLST) and whole-genome sequencing analysis, the species is divided into >100 clonal complexes (CCs) and sub-lineages (SLs) [204–206]. Among the lineages and serotypes, heterogeneity also exists with respect to virulence and ecological niche preferences [27,207]. Three serotypes belonging to lineage I (4b and 1/2b) and lineage II (1/2a) account for >95% of human listeriosis cases [208,209]. Furthermore, among the serotypes associated with human disease, serotype 4b strains are the most frequently implicated in severe clinical outcomes such as brain and placental infections [209,210]. On the other hand, lineage II strains are predominant in foods [209,211].

The molecular basis of *L. monocytogenes* strain and lineage virulence heterogeneity has been deciphered from the genetic differences between the so-called hypervirulent (serotype 4b, lineage I) and the hypovirulent (lineage II) strains [27,208]. Based on single nucleotide polymorphisms (SNPs) and multilocus genotyping (MLGT) using virulence (such as *inlA*, *inlB*; *hly*, *plcC*; *actA*) and *sigB* as well as whole-genome sequencing, several studies have shown that lineage II strains carry numerous mutations in their *inlA* genes that lead to premature stop codons and the production of truncated forms of *inlA* [212–214]. Consequently, despite their frequent occurrence in foods, lineage II strains are hypovirulent due to their inability to express a functional InlA protein needed for a successful systemic infection [27]. Apart from the core virulence genes encoded on LIPI-1 and the *inlAB* islet universally present in all *L. monocytogenes* strains, some lineage I strains harbor an extra set of virulence genes (the *Listeria* Pathogenicity Island 3 (LIPI-3)) [215,216]. LIPI-3 carries a gene cluster that includes the *lIsA* gene conceding for the synthesis of Listeriolysin S (LLS), a bacteriocin whose function is to inhibit host microbiota during infection [216]. The absence of the LIPI-3 in the genomes of lineage II strains and its presence in the sub-lineages of

lineage I (4b serotype) strains suggests that it is the main factor behind the hypervirulence of serotype 4b strains [27,204].

With respect to lineage II strains, their overrepresentation in the food environment is presumed to be a function of their ability to withstand environmental stress [203]. Available evidence shows that stress resistance phenotypes in *L. monocytogenes* are linked to genetic lineages, with lineage II strains particularly showing a better adaptation to environmental stresses such as salt, acid, and heat [217,218]. Using comparative genomics, of 174 clinical and food isolates, Pirone-Davies et al. [219] identified eight plasmid-borne genes uniquely associated with lineage II strains from food. These genes included cadmium resistance genes *cadA* and *cadC*, a multi-drug resistance gene *ebrB*, and a quaternary ammonium compound resistance gene *qac* [219]. Plasmid-harboring *L. monocytogenes* strains were found to be persistent in food processing environments and tolerant to benzalkonium chloride, elevated temperature, salinity, and acidic environments [220–222].

The near-total lack of association of lineage III strains with either foods or human infections is a subject that is still to be fully elucidated. A pan-genome analysis of 26 strains representing lineages I, II, and III, identified 86 disparately distributed genes highly conserved in lineages I and II genomes but highly divergent or absent in lineage III genomes [208]. Among the disparately distributed genes were genes involved in carbohydrate metabolism (phosphotransferase system (PTS)) and transcription factors [208]. Cerutti et al. [223] also identified genes for small regulatory RNAs that co-evolved with genes for pathogenicity and host interaction present in the genomes of lineage I and II strains but missing in the genomes of lineage III strains. Thus, reinforcing the hypothesis that lineage III strains evolved by loss of virulence and metabolic functions [208,223].

7. Conclusions and Future Perspectives

Adaptive stress tolerance responses play a critical role in the pathogenicity of *L. monocytogenes*. While stress adaptation is primarily a mechanism of environmental survival, the processes play a role in protecting the organism against the innate defence systems of the GIT. Furthermore, the transcriptional regulator of environmental stress adaptation, SigB, also has some concurrent effects on the expression of virulence factors that are also under the virulence regulator, PrfA. In parallel with the SigB regulatory effect on virulence genes, PrfA also exerts a synchronic effect on stress response genes for survival in the GIT. The regulatory overlap between the stress response and virulence serves as a point of coordination that facilitates a smooth transition from the avirulent saprophytic survival state to a virulent pathogenic state once inside the host.

Apart from the overlapping functions, direct and indirect interactions between the two transcriptional regulators account for the intricate link between the regulatory networks for stress response and virulence. While a significant amount of information is now available on the expressional crosstalk between SigB and PrfA as the respective central regulators of stress response and virulence, the full understanding of these molecular interactions is still elusive. As a prominent foodborne pathogen, an understanding of the molecular basis of *L. monocytogenes* stress survival and its influence on pathogenesis is critical to the identification of potential targets for the control of the pathogen through the interruption of its transmission and infection cycle.

Author Contributions: Conceptualization, T.S. and E.M.B.; writing—original draft preparation, T.S.; writing—review and editing, T.S. and E.M.B.; supervision, E.M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Linke, K.; Ruckerl, I.; Brugger, K.; Karpiskova, R.; Walland, J.; Muri-Klinger, S.; Tichy, A.; Wagner, M.; Stessl, B. Reservoirs of *Listeria* species in three environmental ecosystems. *Appl. Environ. Microbiol.* **2014**, *80*, 5583–5592. [[CrossRef](#)]
2. Halbedel, S.; Wilking, H.; Holzer, A.; Kleta, S.; Fischer, M.A.; Lüth, S.; Pietzka, A.; Huhulescu, S.; Lachmann, R.; Krings, A.; et al. Large nationwide outbreak of invasive listeriosis associated with blood sausage, Germany, 2018–2019. *Emerg. Infect. Dis.* **2020**, *26*, 1456–1464. [[CrossRef](#)]
3. Thomas, J.; Govender, N.; McCarthy, K.M.; Erasmus, L.K.; Doyle, T.J.; Allam, M.; Ismail, A.; Ramalwa, N.; Sekwadi, P.; Ntshoe, G.; et al. Outbreak of listeriosis in South Africa associated with processed meat. *N. Engl. J. Med.* **2020**, *382*, 632–643. [[CrossRef](#)]
4. Self, J.L.; Conrad, A.; Stroika, S.; Jackson, A.; Whitlock, L.; Jackson, K.A.; Al, J.L.S.E.; Wellman, A.; Fatica, M.K.; Bidol, S.; et al. Multistate outbreak of listeriosis associated with packaged leafy green salads, United States and Canada, 2015–2016. *Emerg. Infect. Dis.* **2019**, *25*, 1461–1468. [[CrossRef](#)] [[PubMed](#)]
5. Warriner, K.; Namvar, A. What is the hysteria with *Listeria*? *Trends Food Sci. Technol.* **2009**, *20*, 245–254. [[CrossRef](#)]
6. Quereda, J.J.; Morón-García, A.; Palacios-Gorba, C.; Dessaux, C.; Portillo, F.G.-D.; Pucciarelli, M.G.; Ortega, A.D. Pathogenicity and virulence of *Listeria monocytogenes*: A trip from environmental to medical microbiology. *Virulence* **2021**, *12*, 2509–2545. [[CrossRef](#)] [[PubMed](#)]
7. Disson, O.; Lecuit, M. Targeting of the central nervous system by *Listeria monocytogenes*. *Virulence* **2012**, *3*, 213–221. [[CrossRef](#)]
8. Pizarro-Cerdá, J.; Cossart, P. Invasion of host cells by *Listeria monocytogenes*. In *Listeria monocytogenes: Pathogenesis and Host Response*; Goldfine, H., Shen, H., Eds.; Springer Science Business Media, LLC: Berlin, Germany, 2007; pp. 159–176.
9. Cossart, P.; Lebreton, A. A trip in the “new Microbiology” with the bacterial pathogen *Listeria monocytogenes*. *FEBS Lett.* **2014**, *588*, 2437–2445. [[CrossRef](#)]
10. Wiktorczyk-Kapischke, N.; Skowron, K.; Grudlewska-Buda, K.; Wałęcka-Zacharska, E.; Korkus, J.; Gospodarek-Komkowska, E. Adaptive response of *Listeria monocytogenes* to the stress factors in the food processing environment. *Front. Microbiol.* **2021**, *12*, 710085. [[CrossRef](#)] [[PubMed](#)]
11. Vorob'eva, L.I. Stressors, stress reactions, and survival of bacteria: A review. *Appl. Biochem. Microbiol.* **2004**, *40*, 217–224. [[CrossRef](#)]
12. Guerreiro, D.N.; Arcari, T.; O'Byrne, C.P. The σ B-mediated general stress response of *Listeria monocytogenes*: Life and death decision making in a pathogen. *Front. Microbiol.* **2020**, *11*, 1505. [[CrossRef](#)]
13. Bucur, F.I.; Grigore-Gurgu, L.; Crauwels, P.; Riedel, C.U.; Nicolau, A.I. Resistance of *Listeria monocytogenes* to stress conditions encountered in food and food processing environments. *Front. Microbiol.* **2018**, *9*, 2700. [[CrossRef](#)]
14. Fang, F.C.; Frawley, E.R.; Tapscott, T.; Vázquez-Torres, A. Bacterial stress responses during host infection. *Cell Host Microbe.* **2016**, *20*, 133–143. [[CrossRef](#)] [[PubMed](#)]
15. Begley, M.; Hill, C. Stress adaptation in foodborne pathogens. *Annu. Rev. Food Sci. Technol.* **2015**, *6*, 191–210. [[CrossRef](#)]
16. Gahan, C.G.M.; Hill, C. *Listeria monocytogenes*: Survival and adaptation in the gastrointestinal tract. *Front. Cell Infect. Microbiol.* **2014**, *4*, 9. [[CrossRef](#)] [[PubMed](#)]
17. Kazmierczak, M.J.; Mithoe, S.C.; Boor, K.J.; Wiedmann, M. *Listeria monocytogenes* σ B regulates stress response and virulence functions. *J. Bacteriol.* **2003**, *185*, 5722–5734. [[CrossRef](#)] [[PubMed](#)]
18. Kazmierczak, M.J.; Wiedmann, M.; Boor, K.J. Contributions of *Listeria monocytogenes* σ B and PrfA to expression of virulence and stress response genes during extra- and intracellular growth. *Microbiology* **2006**, *152*, 1827–1838. [[CrossRef](#)] [[PubMed](#)]
19. Gaballa, A.; Guariglia-Oropeza, V.; Wiedmann, M.; Boor, K.J. Cross talk between SigB and PrfA in *Listeria monocytogenes* facilitates transitions between extra- and intracellular environments. *Microbiol. Mol. Biol. Rev.* **2019**, *83*, e00034-19. [[CrossRef](#)] [[PubMed](#)]
20. Liu, Y.; Orsi, R.H.; Gaballa, A.; Wiedmann, M.; Boor, K.J.; Guariglia-Oropeza, V. Systematic review of the *Listeria monocytogenes* σ B regulon supports a role in stress response, virulence and metabolism. *Future Microbiol.* **2019**, *14*, 801–828. [[CrossRef](#)]
21. Tiensuu, T.; Guerreiro, D.N.; Oliveira, A.H.; O'Byrne, C.; Johansson, J. Flick of a switch: Regulatory mechanisms allowing *Listeria monocytogenes* to transition from a saprophyte to a killer. *Microbiology* **2019**, *165*, 819–833. [[CrossRef](#)] [[PubMed](#)]
22. Drolia, R.; Bhunia, A.K. Crossing the intestinal barrier via *Listeria* adhesion protein and Internalin A. *Trends Microbiol.* **2019**, *27*, 408–425. [[CrossRef](#)]
23. McMullen, P.D.; Freitag, N.E. *Listeria monocytogenes*. In *Molecular Medical Microbiology*, 2nd ed.; Tang, Y.-W., Sussman, M., Liu, D., Poxton, I., Schwartzman, J., Eds.; Academic Press, Elsevier Ltd.: New York, NY, USA, 2014; pp. 1345–1361.
24. Lecuit, M. *Listeria monocytogenes*, a model in infection biology. *Cell. Microbiol.* **2020**, *22*, e13186. [[CrossRef](#)]
25. Liu, D.; Yin, X.; Olyha, S.J.; Nascimento, M.S.L.; Chen, P.; White, T.; Gowthaman, U.; Zhang, T.; Gertie, J.A.; Zhang, B.; et al. IL-10-dependent crosstalk between murine marginal zone B cells, macrophages, and CD8 α ⁺ dendritic cells promotes *Listeria monocytogenes* infection. *Immunity* **2019**, *51*, 64–76. [[CrossRef](#)]
26. Travier, L.; Guadagnini, S.; Gouin, E.; Dufour, A.; Chenal-Francois, V.; Cossart, P.; Olivo-Marin, J.C.; Ghigo, J.M.; Disson, O.; Lecuit, M. ActA promotes *Listeria monocytogenes* aggregation, intestinal colonization and carriage. *PLoS Pathog.* **2013**, *9*, e1003131. [[CrossRef](#)]
27. Disson, O.; Moura, A.; Lecuit, M. Making sense of the biodiversity and virulence of *Listeria monocytogenes*. *Trends Microbiol.* **2021**, *29*, 811–822. [[CrossRef](#)] [[PubMed](#)]
28. de las Heras, A.; Cain, R.J.; Bielecka, M.K.; Vázquez-Boland, J.A. Regulation of *Listeria* virulence: PrfA master and commander. *Curr. Opin. Microbiol.* **2011**, *14*, 118–127. [[CrossRef](#)] [[PubMed](#)]

29. Jagadeesan, B.; Littlejohn, A.E.F.; Amalaradjou, M.A.R.; Singh, A.K.; Mishra, K.K.; La, D.; Kihara, D.; Bhunia, A.K. N-Terminal Gly224-Gly411 domain in *Listeria* adhesion protein interacts with host receptor Hsp60. *PLoS ONE* **2011**, *6*, e20694. [[CrossRef](#)]
30. Pandiripally, V.K.; Westbrook, D.G.; Sunki, G.R.; Bhunia, A.K. Surface protein p104 is involved in adhesion of *Listeria monocytogenes* to human intestinal cell line, Caco-2. *J. Med. Microbiol.* **1999**, *48*, 117–124. [[CrossRef](#)]
31. Burkholder, K.M.; Bhunia, A.K. *Listeria monocytogenes* uses *Listeria* adhesion protein (LAP) to promote bacterial transepithelial translocation and induces expression of LAP receptor Hsp60. *Infect. Immun.* **2010**, *78*, 5062–5073. [[CrossRef](#)]
32. Jagadeesan, B.; Koo, O.K.; Kim, K.P.; Burkholder, K.M.; Mishra, K.K.; Aroonnuan, A.; Bhunia, A.K. LAP, an alcohol acetaldehyde dehydrogenase enzyme in *Listeria*, promotes bacterial adhesion to enterocyte-like Caco-2 cells only in pathogenic species. *Microbiology* **2010**, *156*, 2782–2795. [[CrossRef](#)] [[PubMed](#)]
33. Burkholder, K.M.; Kim, K.-P.; Mishra, K.K.; Medina, S.; Hahm, B.-K.; Kim, H.; Bhunia, A.K. Expression of LAP, a SecA2-dependent secretory protein, is induced under anaerobic environment. *Microbes Infect.* **2009**, *11*, 859–867. [[CrossRef](#)]
34. Drolia, R.; Tenguria, S.; Durkes, A.C.; Turner, J.R.; Bhunia, A.K. *Listeria* adhesion protein induces intestinal epithelial barrier dysfunction for bacterial translocation. *Cell Host Microbe* **2018**, *23*, 470–484.e7. [[CrossRef](#)] [[PubMed](#)]
35. Hymes, J.P.; Klaenhammer, T.R. Stuck in the middle: Fibronectin-binding proteins in Gram-positive bacteria. *Front. Microbiol.* **2016**, *7*, 1504. [[CrossRef](#)] [[PubMed](#)]
36. Henderson, B.; Nair, S.; Pallas, J.; Williams, M.A. Fibronectin: A multidomain host adhesin targeted by bacterial fibronectin-binding proteins. *FEMS Microbiol. Rev.* **2011**, *35*, 147–200. [[CrossRef](#)]
37. Dramsi, S.; Bourdichon, F.; Cabanes, D.; Lecuit, M.; Fsihi, H.; Cossart, P. FbpA, a novel multifunctional *Listeria monocytogenes* virulence factor. *Mol. Microbiol.* **2004**, *53*, 639–649. [[CrossRef](#)]
38. Gaillard, J.-L.; Berche, P.; Frehel, C.; Gouln, E.; Cossart, P. Entry of *L. monocytogenes* into cells is mediated by internalin, a repeat protein reminiscent of surface antigens from Gram-positive cocci. *Cell* **1991**, *65*, 1127–1141. [[CrossRef](#)]
39. Ireton, K.; Mortuza, R.; Gyanwali, G.C.; Gianfelice, A.; Hussain, M. Role of internalin proteins in the pathogenesis of *Listeria monocytogenes*. *Mol. Microbiol.* **2021**, *116*, 1407–1419. [[CrossRef](#)]
40. Schubert, W.-D.; Urbanke, C.; Ziehm, T.; Beier, V.; Machner, M.P.; Domann, E.; Wehland, J.; Chakraborty, T.; Heinz, D.W. Structure of internalin, a major invasion protein of *Listeria monocytogenes*, in complex with its human receptor E-cadherin. *Cell* **2002**, *111*, 825–836. [[CrossRef](#)]
41. Dellaflora, L.; Filipello, V.; Dall’Asta, C.; Finazzi, G.; Galaverna, G.; Losio, M.N. A structural study on the *Listeria monocytogenes* internalin A—Human E-cadherin interaction: A molecular tool to investigate the effects of missense mutations. *Toxins* **2020**, *12*, 60. [[CrossRef](#)] [[PubMed](#)]
42. Braun, L.; Dramsi, S.; Dehoux, P.; Bierne, H.; Lindahl, G.; Cossart, P. InIB: An invasion protein of *Listeria monocytogenes* with a novel type of surface association. *Mol. Microbiol.* **1997**, *25*, 285–294. [[CrossRef](#)] [[PubMed](#)]
43. Bierne, H.; Sabet, C.; Personnic, N.; Cossart, P. Internalins: A complex family of leucine-rich repeat-containing proteins in *Listeria monocytogenes*. *Microbes Infect.* **2007**, *9*, 1156–1166. [[CrossRef](#)] [[PubMed](#)]
44. Pizarro-Cerdá, J.; Kühbacher, A.; Cossart, P. Entry of *Listeria monocytogenes* in mammalian epithelial cells: An updated view. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a010009. [[CrossRef](#)]
45. Milohanic, E.; Glaser, P.; Coppée, J.-Y.; Frangeul, L.; Vega, Y.; Vázquez-Boland, J.A.; Kunst, F.; Cossart, P.; Buchrieser, C. Transcriptome analysis of *Listeria monocytogenes* identifies three groups of genes differently regulated by PrfA. *Mol. Microbiol.* **2003**, *47*, 1613–1625. [[CrossRef](#)]
46. Hamon, M.; Ribet, D.; Stavru, F.; Cossart, P. Listeriolysin O: The Swiss army knife of *Listeria*. *Trends Microbiol.* **2012**, *20*, 360–368. [[CrossRef](#)]
47. Hof, H. Virulence of different strains of *Listeria monocytogenes* serovar 1/2a. *Med. Microbiol. Immunol.* **1984**, *173*, 207–218. [[CrossRef](#)]
48. Geoffroy, C.; Gaillard, J.-L.; Alouf, J.E.; Berche, P. Purification, characterization, and toxicity of the sulfhydryl-activated hemolysin Listerion O from *Listeria monocytogenes*. *Infect. Immun.* **1987**, *55*, 1641–1646. [[CrossRef](#)] [[PubMed](#)]
49. Kuhn, M.; Kathariou, S.; Goebel, W. Hemolysin supports survival but not entry of the intracellular bacterium *Listeria monocytogenes*. *Infect. Immun.* **1988**, *56*, 79–82. [[CrossRef](#)] [[PubMed](#)]
50. Phelps, C.C.; Vadia, S.; Arnett, E.; Tan, Y.; Zhang, X.; Pathak-Sharma, S.; Gavrilin, M.A.; Seveau, S. Relative roles of Listeriolysin O, InlA, and InlB in *Listeria monocytogenes* uptake by host cells. *Infect. Immun.* **2018**, *86*, e00555-18. [[CrossRef](#)] [[PubMed](#)]
51. Camilli, A.; Goldfine, H.; Portnoy, D.A. *Listeria monocytogenes* mutants lacking phosphatidylinositol-specific phospholipase C are avirulent. *J. Exp. Med.* **1991**, *173*, 751–754. [[CrossRef](#)]
52. Smith, G.A.; Marquis, H.; Jones, S.; Johnston, N.C.; Portnoy, D.A.; Goldfine, H. The two distinct phospholipases C of *Listeria monocytogenes* have overlapping roles in escape from a vacuole and cell-to-cell spread. *Infect. Immun.* **1995**, *63*, 4231–4237. [[CrossRef](#)]
53. Poussin, M.A.; Goldfine, H. Involvement of *Listeria monocytogenes* phosphatidylinositol-specific phospholipase C and host protein kinase C in permeabilization of the macrophage phagosome. *Infect. Immun.* **2005**, *73*, 4410–4413. [[CrossRef](#)]
54. Gründling, A.; Gonzalez, M.D.; Higgins, D.E. Requirement of the *Listeria monocytogenes* broad-range phospholipase PC-PLC during infection of human epithelial cells. *J. Bacteriol.* **2003**, *185*, 6295–6307.
55. Coffey, A.; Burg, B.V.D.; Veltman, R.; Abee, T. Characteristics of the biologically active 35-kDa metalloprotease virulence factor from *Listeria monocytogenes*. *J. Appl. Microbiol.* **2000**, *88*, 132–141. [[CrossRef](#)] [[PubMed](#)]

56. Suárez, M.; González-Zorn, B.; Vega, Y.; Chico-Calero, I.; Vázquez-Boland, J.A. A role for ActA in epithelial cell invasion by *Listeria monocytogenes*. *Cell. Microbiol.* **2001**, *3*, 853–864. [[CrossRef](#)] [[PubMed](#)]
57. Kocks, C.; Hellio, R.; Gounon, P.; Ohayon, H.; Cossart, P. Polarized distribution of *Listeria monocytogenes* surface protein ActA at the site of directional actin assembly. *J. Cell Sci.* **1993**, *105*, 699–710. [[CrossRef](#)] [[PubMed](#)]
58. Travier, L.; Lecuit, M. *Listeria monocytogenes* ActA: A new function for a “classic” virulence factor. *Curr. Opin. Microbiol.* **2014**, *17*, 53–60. [[CrossRef](#)] [[PubMed](#)]
59. Skoble, J.; Auerbuch, V.; Goley, E.D.; Welch, M.D.; Portnoy, D.A. Pivotal role of VASP in Arp2/3 complex-mediated actin nucleation, actin branch-formation, and *Listeria monocytogenes* motility. *J. Cell Biol.* **2001**, *155*, 89–100. [[CrossRef](#)] [[PubMed](#)]
60. Kühn, S.; Enninga, J. The actin comet guides the way: How *Listeria* actin subversion has impacted cell biology, infection biology and structural biology. *Cell. Microbiol.* **2020**, *22*, e13190. [[CrossRef](#)] [[PubMed](#)]
61. Maurella, C.; Gallina, S.; Ru, G.; Adriano, D.; Bellio, A.; Bianchi, D.M.; Chiavacci, L.; Crescio, M.I.; Croce, M.; D’Errico, V.; et al. Outbreak of febrile gastroenteritis caused by *Listeria monocytogenes* 1/2a in sliced cold beef ham, Italy, May 2016. *Eurosurveillance* **2018**, *23*, 17–00155. [[CrossRef](#)]
62. Ooi, S.T.; Lorber, B. Gastroenteritis due to *Listeria monocytogenes*. *Clin. Infect. Dis.* **2005**, *40*, 1327–1332. [[CrossRef](#)] [[PubMed](#)]
63. Jacks, A.; Pihlajasaari, A.; Vahe, M.; Myntti, A.; Kaukoranta, S.-S.; Elomaa, N.; Salmenlinna, S.; Rantala, L.; Lahti, K.; Huusko, S.; et al. Outbreak of hospital-acquired gastroenteritis and invasive infection caused by *Listeria monocytogenes*, Finland, 2012. *Epidemiol. Infect.* **2016**, *144*, 2732–2742. [[CrossRef](#)]
64. Sim, J.; Hood, D.; Finnie, L.; Wilson, M.; Graham, C.; Brett, M.; Hudson, J. Series of incidents of *Listeria monocytogenes* non-invasive febrile gastroenteritis involving ready-to-eat meats. *Lett. Appl. Microbiol.* **2002**, *35*, 409–413. [[CrossRef](#)]
65. Halbedel, S.; Prager, R.; Banerji, S.; Kleta, S.; Trost, E.; Nishanth, G.; Alles, G.; Hölzel, C.; Schlesiger, F.; Pietzka, A.; et al. A *Listeria monocytogenes* ST2 clone lacking chitinase ChiB from an outbreak of non-invasive gastroenteritis. *Emerg. Microbes Infect.* **2019**, *8*, 17–28. [[CrossRef](#)]
66. Radoshevich, L.; Cossart, P. *Listeria monocytogenes*: Towards a complete picture of its physiology and pathogenesis. *Nat. Rev. Microbiol.* **2018**, *16*, 32–46. [[CrossRef](#)]
67. Nikitas, G.; Deschamps, C.; Disson, O.; Niault, T.; Cossart, P.; Lecuit, M. Transcytosis of *Listeria monocytogenes* across the intestinal barrier upon specific targeting of goblet cell accessible E-cadherin. *J. Exp. Med.* **2011**, *208*, 2263–2277. [[CrossRef](#)] [[PubMed](#)]
68. Pentecost, M.; Otto, G.; Theriot, J.; Amieva, M.R. *Listeria monocytogenes* invades the epithelial junctions at sites of cell extrusion. *PLoS Pathog.* **2006**, *2*, 0029–0040. [[CrossRef](#)]
69. Bonazzi, M.; Lecuit, M.; Cossart, P. *Listeria monocytogenes* internalin and E-cadherin: From structure to pathogenesis. *Cell. Microbiol.* **2009**, *11*, 693–702. [[CrossRef](#)] [[PubMed](#)]
70. Saila, S.; Gyanwali, G.C.; Hussain, M.; Gianfelice, A.; Ireton, K. The host GTPase Arf1 and its effectors AP1 and PICK1 stimulate actin polymerization and exocytosis to promote entry of *Listeria monocytogenes*. *Infect. Immun.* **2020**, *88*, e00578-19. [[CrossRef](#)] [[PubMed](#)]
71. Holch, A.; Ingmer, H.; Licht, T.R.; Gram, L. *Listeria monocytogenes* strains encoding premature stop codons in *inlA* invade mice and guinea pig fetuses in orally dosed dams. *J. Med. Microbiol.* **2013**, *62*, 1799–1806. [[CrossRef](#)]
72. Gelbíčová, T.; Kolářčková, I.; Pantůček, R.; Karpíšková, R. A novel mutation leading to a premature stop codon in *inlA* of *Listeria monocytogenes* isolated from neonatal listeriosis. *New Microbiol.* **2015**, *38*, 293–296.
73. Hase, K.; Kawano, K.; Nochi, T.; Pontes, G.S.; Fukuda, S.; Ebisawa, M.; Kadokura, K.; Tobe, T.; Fujimura, Y.; Kawano, S.; et al. Uptake through glycoprotein 2 of FimH+ bacteria by M cells initiates mucosal immune response. *Nature* **2009**, *462*, 226–230. [[CrossRef](#)] [[PubMed](#)]
74. Rey, C.; Chang, Y.-Y.; Latour-Lambert, P.; Varet, H.; Proux, C.; Legendre, R.; Coppée, J.-Y.; Enninga, J. Transcytosis subversion by M cell-to-enterocyte spread promotes *Shigella flexneri* and *Listeria monocytogenes* intracellular bacterial dissemination. *PLoS Pathog.* **2020**, *16*, e1008446. [[CrossRef](#)] [[PubMed](#)]
75. Marco, A.J.; Altimira, J.; Prats, N.; López, S.; Dominguez, L.; Domingo, M.; Briones, V. Penetration of *Listeria monocytogenes* in mice infected by the oral route. *Microb. Pathog.* **1997**, *23*, 255–263. [[CrossRef](#)] [[PubMed](#)]
76. Corr, S.; Hill, C.; Gahan, C.G. An in vitro cell-culture model demonstrates internalin- and hemolysin-independent translocation of *Listeria monocytogenes* across M cells. *Microb. Pathog.* **2006**, *41*, 241–250. [[CrossRef](#)] [[PubMed](#)]
77. Charlier, C.; Disson, O.; Lecuit, M. Maternal-neonatal listeriosis. *Virulence* **2020**, *11*, 391–397. [[CrossRef](#)]
78. Disson, O.; Grayo, S.; Huillet, E.; Nikitas, G.; Langa-Vives, F.; Dussurget, O.; Ragon, M.; Le Monnier, A.; Babinet, C.; Cossart, P.; et al. Conjugated action of two species-specific invasion proteins for fetoplacental listeriosis. *Nat. Lett.* **2008**, *455*, 1114–1118. [[CrossRef](#)] [[PubMed](#)]
79. Kortebi, M.; Milohanic, E.; Mitchell, G.; Péchoux, C.; Prevost, M.-C.; Cossart, P.; Bierne, H. *Listeria monocytogenes* switches from dissemination to persistence by adopting a vacuolar lifestyle in epithelial cells. *PLoS Pathog.* **2017**, *13*, e1006734. [[CrossRef](#)] [[PubMed](#)]
80. Schnupf, P.; Portnoy, D.A. Listeriolysin O: A phagosome-specific lysin. *Microbes Infect.* **2007**, *9*, 1176–1187. [[CrossRef](#)] [[PubMed](#)]
81. Charlier, C.; Perrodeau, É.; Leclercq, A.; Cazenave, B.; Pilmis, B.; Henry, B.; Lopes, A.; Maury, M.M.; Moura, A.; Goffinet, F.; et al. Clinical features and prognostic factors of listeriosis: The MONALISA national prospective cohort study. *Lancet Infect. Dis.* **2017**, *17*, 510–519. [[CrossRef](#)]

82. de Noordhout, C.M.; Devleeschauwer, B.; Angulo, F.J.; Verbeke, G.; Haagsma, J.; Kirk, M.; Havelaar, A.; Speybroeck, N. The global burden of listeriosis: A systematic review and meta-analysis. *Lancet Infect. Dis.* **2014**, *14*, 1073–1082. [[CrossRef](#)]
83. Scobie, A.; Kanagarajah, S.; Harris, R.J.; Byrne, L.; Amar, C.; Grant, K.; Godbole, G. Mortality risk factors for listeriosis—A 10 year review of non-pregnancy associated cases in England 2006–2015. *J. Infect.* **2019**, *78*, 208–214. [[CrossRef](#)] [[PubMed](#)]
84. Wadhwa Desai, R.; Smith, M.A. Pregnancy-related listeriosis. *Birth Defects Res.* **2017**, *109*, 324–335. [[CrossRef](#)]
85. Lepe, J.A. Current aspects of listeriosis. *Med. Clínica* **2020**, *154*, 453–458. [[CrossRef](#)] [[PubMed](#)]
86. Shoai-Tehrani, M.; Pilmis, B.; Maury, M.M.; Robineau, O.; Disson, O.; Jouvion, G.; Coulpier, G.; Thouvenot, P.; Bracq-Dieye, H.; Valès, G.; et al. *Listeria monocytogenes*-associated endovascular infections: A study of 71 consecutive cases. *J. Infect.* **2019**, *79*, 322–331. [[CrossRef](#)]
87. Morgand, M.; Leclercq, A.; Maury, M.; Bracq-Dieye, H.; Thouvenot, P.; Vales, G.; Lecuit, M.; Charlier, C. *Listeria monocytogenes*-associated respiratory infections: A study of 38 consecutive cases. *Clin. Microbiol. Infect.* **2018**, *24*, 1339–e1. [[CrossRef](#)]
88. Charlier, C.; Fevre, C.; Travier, L.; Cazenave, B.; Bracq-Dieye, H.; Podevin, J.; Assomany, D.; Guilbert, L.; Bossard, C.; Carpentier, F.; et al. *Listeria monocytogenes*-associated biliary tract infections: A study of 12 consecutive cases and review. *Medicine* **2014**, *93*, e105. [[CrossRef](#)] [[PubMed](#)]
89. Charlier, C.; Leclercq, A.; Cazenave, B.; Desplaces, N.; Travier, L.; Cantinelli, T.; Lortholary, O.; Goulet, V.; Le Monnier, A.; Lecuit, M.; et al. *Listeria monocytogenes*-associated joint and bone infections: A study of 43 consecutive cases. *Clin. Infect. Dis.* **2012**, *54*, 240–248. [[CrossRef](#)] [[PubMed](#)]
90. Wesche, A.M.; Gurtler, J.B.; Marks, B.P.; Ryser, E.T. Stress, sublethal injury, resuscitation, and virulence of bacterial foodborne pathogens. *J. Food Prot.* **2009**, *72*, 1121–1138. [[CrossRef](#)]
91. Singh, S.; Shalini, R. Effect of Hurdle Technology in Food Preservation: A Review. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 641–649. [[CrossRef](#)] [[PubMed](#)]
92. Chorianopoulos, N.; Giaouris, E.; Grigoraki, I.; Skandamis, P.; Nychas, G.-J. Effect of acid tolerance response (ATR) on attachment of *Listeria monocytogenes* Scott A to stainless steel under extended exposure to acid or/and salt stress and resistance of sessile cells to subsequent strong acid challenge. *Int. J. Food Microbiol.* **2011**, *145*, 400–406. [[CrossRef](#)]
93. Davis, M.J.; Coote, P.J.; O’Byrne, C.P. Acid tolerance in *Listeria monocytogenes*: The adaptive acid tolerance response (ATR) and growth-phase-dependent acid resistance. *Microbiology* **1996**, *142*, 2975–2982. [[CrossRef](#)] [[PubMed](#)]
94. O’Driscoll, B.; Gahan, C.G.M.; Hill, C. Adaptive acid tolerance response in *Listeria monocytogenes*: Isolation of an acid-tolerant mutant which demonstrates increased virulence. *Appl. Environ. Microbiol.* **1996**, *62*, 1693–1698. [[CrossRef](#)]
95. Abeyesundara, P.D.A.; Nannapaneni, R.; Soni, K.A.; Sharma, C.S.; Mahmoud, B. Induction and stability of oxidative stress adaptation in *Listeria monocytogenes* EGD (Bug600) and F1057 in sublethal concentrations of H₂O₂ and NaOH. *Int. J. Food Microbiol.* **2016**, *238*, 288–294. [[CrossRef](#)] [[PubMed](#)]
96. Sibanda, T.; Buys, E.M. Modelling the survival of *Listeria monocytogenes* strains in soft lactic cheese following acid and salt stress exposures. *Lett. Appl. Microbiol.* **2019**, *69*, 230–236. [[CrossRef](#)] [[PubMed](#)]
97. Skandamis, P.N.; Yoon, Y.; Stopforth, J.D.; Kendall, P.A.; Sofos, J.N. Heat and acid tolerance of *Listeria monocytogenes* after exposure to single and multiple sublethal stresses. *Food Microbiol.* **2008**, *25*, 294–303. [[CrossRef](#)] [[PubMed](#)]
98. Faleiro, M.L.; Andrew, P.W.; Power, D. Stress response of *Listeria monocytogenes* isolated from cheese and other foods. *Int. J. Food Microbiol.* **2003**, *84*, 207–216. [[CrossRef](#)]
99. Alvarez-Ordóñez, A.; Broussolle, V.; Colin, P.; Nguyen-The, C.; Prieto, M. The adaptive response of bacterial food-borne pathogens in the environment, host and food: Implications for food safety. *Int. J. Food Microbiol.* **2015**, *213*, 99–109. [[CrossRef](#)] [[PubMed](#)]
100. Phadtare, S. Recent developments in bacterial cold-shock response. *Curr. Issues Mol. Biol.* **2004**, *6*, 125–136. [[PubMed](#)]
101. Roncarati, D.; Scarlato, V. Regulation of heat-shock genes in bacteria: From signal sensing to gene expression output. *FEMS Microbiol. Rev.* **2017**, *41*, 549–574. [[CrossRef](#)]
102. Ryan, S.; Begley, M.; Gahan, C.G.M.; Hill, C. Molecular characterization of the arginine deiminase system in *Listeria monocytogenes*: Regulation and role in acid tolerance. *Environ. Microbiol.* **2009**, *11*, 432–445. [[CrossRef](#)] [[PubMed](#)]
103. Tasara, T.; Stephan, R. Cold stress tolerance of *Listeria monocytogenes*: A review of molecular adaptive mechanisms and food safety implications. *J. Food Prot.* **2006**, *69*, 1473–1484. [[CrossRef](#)]
104. Cotter, P.D.; O’Reilly, K.; Hill, C. Role of the glutamate decarboxylase acid resistance system in the survival of *Listeria monocytogenes* LO28 in low pH foods. *J. Food Prot.* **2001**, *64*, 1362–1368. [[CrossRef](#)] [[PubMed](#)]
105. Bremer, E.; Krämer, R. Responses of microorganisms to osmotic stress. *Annu. Rev. Microbiol.* **2019**, *73*, 313–334. [[CrossRef](#)] [[PubMed](#)]
106. Yan, N.; Marschner, P.; Cao, W.; Zuo, C.; Qin, W. Influence of salinity and water content on soil microorganisms. *Int. Soil Water Conserv. Res.* **2015**, *3*, 316–323. [[CrossRef](#)]
107. Manzanera, M. Dealing with water stress and microbial preservation. *Environ. Microbiol.* **2021**, *23*, 3351–3359. [[CrossRef](#)]
108. Cole, M.B.; Jones, M.V.; Holyoak, C. The effect of pH, salt concentration and temperature on the survival and growth of *Listeria monocytogenes*. *J. Appl. Microbiol.* **1990**, *69*, 63–72.
109. Angelidis, A.S.; Smith, G.M. Three transporters mediate uptake of glycine betaine and carnitine by *Listeria monocytogenes* in response to hyperosmotic stress. *Appl. Environ. Microbiol.* **2003**, *69*, 1013–1022. [[CrossRef](#)] [[PubMed](#)]
110. Bayles, D.O.; Wilkinson, B.J. Osmoprotectants and cryoprotectants for *Listeria monocytogenes*. *Lett. Appl. Microbiol.* **2000**, *30*, 23–27. [[CrossRef](#)] [[PubMed](#)]

111. Ko, R.; Smith, L.T. Identification of an ATP-driven, osmoregulated glycine betaine transport system in *Listeria monocytogenes*. *Appl. Environ. Microbiol.* **1999**, *65*, 4040–4048. [[CrossRef](#)] [[PubMed](#)]
112. Wood, J.M. Osmosensing by bacteria: Signals and membrane-based sensors. *Microbiol. Mol. Biol. Rev.* **1999**, *63*, 230–262. [[CrossRef](#)] [[PubMed](#)]
113. Gibhardt, J.; Heidemann, J.L.; Bremenkamp, R.; Rosenberg, J.; Seifert, R.; Kaefer, V.; Ficner, R.; Commichau, F.M. An extracytoplasmic protein and a moonlighting enzyme modulate synthesis of c-di-AMP in *Listeria monocytogenes*. *Environ. Microbiol.* **2020**, *22*, 2771–2791. [[CrossRef](#)]
114. Gerhardt, P.N.; Tombras Smith, L.; Smith, G.M. Osmotic and chill activation of glycine betaine porter II in *Listeria monocytogenes* membrane vesicles. *J. Bacteriol.* **2000**, *182*, 2544–2550. [[CrossRef](#)] [[PubMed](#)]
115. Sleator, R.D.; Gahan, C.G.; Abee, T.; Hill, C. Identification and disruption of betL, a secondary glycine betaine transport system linked to the salt tolerance of *Listeria monocytogenes* LO28. *Appl. Environ. Microbiol.* **1999**, *65*, 2078–2083. [[CrossRef](#)] [[PubMed](#)]
116. Sleator, R.D.; Wouters, J.; Gahan, C.G.; Abee, T.; Hill, C. Analysis of the role of OpuC, an osmolyte transport system, in salt tolerance and virulence potential of *Listeria monocytogenes*. *Appl. Environ. Microbiol.* **2002**, *67*, 2692–2698. [[CrossRef](#)]
117. Roe, A.J.; McLaggan, D.; Davidson, I.; O’Byrne, C.; Booth, I.R. Perturbation of anion balance during inhibition of growth of *Escherichia coli* by weak acids. *J. Bacteriol.* **1998**, *180*, 767–772. [[CrossRef](#)] [[PubMed](#)]
118. Kim, S.A.; Rhee, M.S. Marked synergistic bactericidal effects and mode of action of medium-chain fatty acids in combination with organic acids against *Escherichia coli* O157:H7. *Appl. Environ. Microbiol.* **2013**, *79*, 6552–6560. [[CrossRef](#)] [[PubMed](#)]
119. Ning, Y.; Yan, A.; Yang, K.; Wang, Z.; Li, X.; Jia, Y. Antibacterial activity of phenyllactic acid against *Listeria monocytogenes* and *Escherichia coli* by dual mechanisms. *Food Chem.* **2017**, *228*, 533–540. [[CrossRef](#)] [[PubMed](#)]
120. Arcari, T.; Feger, M.-L.; Guerreiro, D.N.; Wu, J.; O’Byrne, C.P. Comparative review of the responses of *Listeria monocytogenes* and *Escherichia coli* to Low pH stress. *Genes* **2020**, *11*, 1330. [[CrossRef](#)]
121. Cotter, P.D.; Ryan, S.; Gahan, C.G.M.; Hill, C. Presence of GadD1 glutamate decarboxylase in selected *Listeria monocytogenes* strains is associated with an ability to grow at low pH. *Appl. Environ. Microbiol.* **2005**, *71*, 2832–2839. [[CrossRef](#)] [[PubMed](#)]
122. Spano, G.; Chiappa, G.; Beneduce, L.; Massa, S. Expression analysis of putative *arcA*, *arcB* and *arcC* genes partially cloned from *Lactobacillus plantarum* isolated from wine. *J. Appl. Microbiol.* **2004**, *96*, 185–193. [[CrossRef](#)]
123. Ryan, S.; Hill, C.; Gahan, C.G.M. Acid stress responses in *Listeria monocytogenes*. In *Advances in Applied Microbiology*; Elsevier Masson SAS: Amsterdam, The Netherlands, 2008; pp. 67–91.
124. Shen, Q.; Jangam, P.M.; Soni, K.A.; Nannapaneni, R.; Schilling, W.; Silva, J.L. Low, medium, and high heat tolerant strains of *Listeria monocytogenes* and increased heat stress resistance after exposure to sublethal heat. *J. Food Prot.* **2014**, *77*, 1298–1307. [[CrossRef](#)] [[PubMed](#)]
125. Haykir, O.; Mohácsi-Farkas, C.; Engelhardt, T. Enhanced heat resistance of *Listeria innocua* as a surrogate of *Listeria monocytogenes* after sublethal heat treatment. *Acta Aliment.* **2022**, *51*, 241–248. [[CrossRef](#)]
126. Lou, Y.; Yousef, A.E. Resistance of *Listeria monocytogenes* to heat after adaptation to environmental stresses. *J. Food Prot.* **1996**, *59*, 465–471. [[CrossRef](#)] [[PubMed](#)]
127. Taormina, P.J.; Beuchat, L.R. Survival and heat resistance of *Listeria monocytogenes* after exposure to alkali and chlorine. *Appl. Environ. Microbiol.* **2001**, *67*, 2555–2563. [[CrossRef](#)] [[PubMed](#)]
128. Van Der Veen, S.; Hain, T.; Wouters, J.A.; Hossain, H.; De Vos, W.M.; Abee, T.; Chakraborty, T.; Wells-Bennik, M.H.J. The heat-shock response of *Listeria monocytogenes* comprises genes involved in heat shock, cell division, cell wall synthesis, and the SOS response. *Microbiology* **2007**, *153*, 3593–3607. [[CrossRef](#)] [[PubMed](#)]
129. Hanawa, T.; Kai, M.; Kamiya, S.; Yamamoto, T. Cloning, sequencing, and transcriptional analysis of the *dnaK* heat shock operon of *Listeria monocytogenes*. *Cell Stress Chaperones* **2000**, *5*, 21–29. [[CrossRef](#)]
130. Gahan, C.G.M.; O’Mahony, J.; Hill, C. Characterization of the *groESL* operon in *Listeria monocytogenes*: Utilization of two reporter systems (*gfp* and *hly*) for evaluating in vivo expression. *Infect. Immun.* **2001**, *69*, 3924–3932. [[CrossRef](#)]
131. Nair, S.; Derré, I.; Msadek, T.; Gaillot, O.; Berche, P. CtsR controls class III heat shock gene expression in the human pathogen *Listeria monocytogenes*. *Mol. Microbiol.* **2000**, *35*, 800–811. [[CrossRef](#)] [[PubMed](#)]
132. Cabrita, P.; Trigo, M.J.; Ferreira, R.B.; Brito, L. Differences in the expression of cold stress-related genes and in the swarming motility among persistent and sporadic strains of *Listeria monocytogenes*. *Foodborne Pathog. Dis.* **2015**, *12*, 576–584. [[CrossRef](#)]
133. Bayles, D.O.; Annous, B.A.; Wilkinson, B.J. Cold stress proteins induced in *Listeria monocytogenes* in response to temperature downshock and growth at low temperatures. *Appl. Environ. Microbiol.* **1996**, *62*, 1116–1119. [[CrossRef](#)]
134. Russell, N.J. Bacterial membranes: The effects of chill storage and food processing. An overview. *Int. J. Food. Microbiol.* **2002**, *79*, 27–34. [[CrossRef](#)]
135. Yoon, Y.; Lee, H.; Lee, S.; Kim, S.; Choi, K.-H. Membrane fluidity-related adaptive response mechanisms of foodborne bacterial pathogens under environmental stresses. *Food Res. Int.* **2015**, *72*, 25–36. [[CrossRef](#)]
136. Annous, B.A.; Becker, L.A.; Bayles, D.O.; Labeda, D.P.; Wilkinson, B.J. Critical role of anteiso-C15:0 fatty acid in the growth of *Listeria monocytogenes* at low temperatures. *Appl. Environ. Microbiol.* **1997**, *63*, 3887–3894. [[CrossRef](#)]
137. Choi, K.H.; Heath, R.J.; Rock, C.O. β -ketoacyl-acyl carrier protein synthase III (FabH) is a determining factor in branched-chain fatty acid biosynthesis. *J. Bacteriol.* **2000**, *182*, 365–370. [[CrossRef](#)]

138. Nelson, K.E.; Fouts, D.E.; Mongodin, E.F.; Ravel, J.; DeBoy, R.T.; Kolonay, J.F.; Rasko, D.A.; Angiuoli, S.V.; Gill, S.R.; Paulsen, I.T.; et al. Whole genome comparisons of serotype 4b and 1/2a strains of the food-borne pathogen *Listeria monocytogenes* reveal new insights into the core genome components of this species. *Nucleic Acids Res.* **2004**, *32*, 2386–2395. [[CrossRef](#)] [[PubMed](#)]
139. Schmid, B.; Klumpp, J.; Raimann, E.; Loessner, M.J.; Stephan, R.; Tasara, T. Role of cold shock proteins in growth of *Listeria monocytogenes* under cold and osmotic stress conditions. *Appl. Environ. Microbiol.* **2009**, *75*, 1621–1627. [[CrossRef](#)] [[PubMed](#)]
140. Wemekamp-Kamphuis, H.H.; Karatzas, A.K.; Wouters, J.A.; Abee, T. Enhanced levels of cold shock proteins in *Listeria monocytogenes* LO28 upon exposure to low temperature and high hydrostatic pressure. *Appl. Environ. Microbiol.* **2002**, *68*, 456–463. [[CrossRef](#)] [[PubMed](#)]
141. Netterling, S.; Vaitkevicius, K.; Nord, S.; Johansson, J. A *Listeria monocytogenes* RNA helicase essential for growth and ribosomal maturation at low temperatures uses its C terminus for appropriate interaction with the ribosome. *J. Bacteriol.* **2012**, *194*, 4377–4385. [[CrossRef](#)]
142. Markkula, A.; Lindstrom, M.; Johansson, P.; Bjorkroth, J.; Korkeala, H. Roles of four putative DEAD-box RNA helicase genes in growth of *Listeria monocytogenes* EGD-e under heat, pH, osmotic, ethanol, and oxidative stress conditions. *Appl. Environ. Microbiol.* **2012**, *78*, 6875–6882. [[CrossRef](#)] [[PubMed](#)]
143. Bäreclöv, C.; Vaitkevicius, K.; Netterling, S.; Johansson, J. DEXD-box RNA-helicases in *Listeria monocytogenes* are important for growth, ribosomal maturation, rRNA processing and virulence factor expression. *RNA Biol.* **2014**, *11*, 1457–1466. [[CrossRef](#)] [[PubMed](#)]
144. Mendum, M.L.; Smith, L.T. Characterization of glycine betaine porter I from *Listeria monocytogenes* and its roles in salt and chill tolerance. *Appl. Environ. Microbiol.* **2002**, *68*, 813–819. [[CrossRef](#)] [[PubMed](#)]
145. Liu, S.; Graham, J.E.; Bigelow, L.; Morse, P.D.; Wilkinson, B.J. Identification of *Listeria monocytogenes* genes expressed in response to growth at low temperature. *Appl. Environ. Microbiol.* **2002**, *68*, 1697–1705. [[CrossRef](#)]
146. Chan, Y.C.; Wiedmann, M. Physiology and genetics of *Listeria monocytogenes* survival and growth at cold temperatures. *Crit. Rev. Food Sci. Nutr.* **2008**, *49*, 237–253. [[CrossRef](#)]
147. Zhao, X.; Drlica, K. Reactive oxygen species and the bacterial response to lethal stress. *Curr. Opin. Microbiol.* **2014**, *21*, 1–6. [[CrossRef](#)]
148. Azizoglu, R.O.; Kathariou, S. Temperature-dependent requirement for catalase in aerobic growth of *Listeria monocytogenes* F2365. *Appl. Environ. Microbiol.* **2010**, *76*, 6998–7003. [[CrossRef](#)] [[PubMed](#)]
149. Suo, Y.; Huang, Y.; Liu, Y.; Shi, C.; Shi, X. The expression of superoxide dismutase (SOD) and a putative ABC transporter permease is inversely correlated during biofilm formation in *Listeria monocytogenes* 4b G. *PLoS ONE* **2012**, *7*, e48467. [[CrossRef](#)] [[PubMed](#)]
150. Mains, D.R.; Eallonardo, S.J.; Freitag, N.E. Identification of *Listeria monocytogenes* genes contributing to oxidative stress resistance under conditions relevant to host infection. *Infect. Immun.* **2021**, *89*, e00700-20. [[CrossRef](#)] [[PubMed](#)]
151. Ruhland, B.R.; Reniere, M.L. Sense and sensor ability: Redox-responsive regulators in *Listeria monocytogenes*. *Curr. Opin. Microbiol.* **2019**, *47*, 20–25. [[CrossRef](#)] [[PubMed](#)]
152. Rea, R.; Hill, C.; Gahan, C.G.M. *Listeria monocytogenes* PerR mutants display a small-colony phenotype, increased sensitivity to hydrogen peroxide, and significantly reduced murine virulence. *Appl. Environ. Microbiol.* **2005**, *71*, 8314–8322. [[CrossRef](#)] [[PubMed](#)]
153. Sleator, R.D.; Watson, D.; Hill, C.; Gahan, C.G.M. The interaction between *Listeria monocytogenes* and the host gastrointestinal tract. *Microbiology* **2009**, *155*, 2463–2475. [[CrossRef](#)]
154. Conte, M.P.; Petrone, G.; Di Biase, A.M.; Ammendolia, M.G.; Superti, F.; Seganti, L. Acid tolerance in *Listeria monocytogenes* influences invasiveness of enterocyte-like cells and macrophage-like cells. *Microb. Pathog.* **2000**, *29*, 137–144. [[CrossRef](#)]
155. Saklani-Jusforgues, H.; Fontan, E.; Goossens, P.L. Effect of acid-adaptation on *Listeria monocytogenes* survival and translocation in a murine intragastric infection model. *FEMS Microbiol. Lett.* **2000**, *193*, 155–159. [[CrossRef](#)]
156. O’Byrne, C.P.; Karatzas, K.A.G. The role of Sigma B (σ_B) in the stress adaptations of *Listeria monocytogenes*: Overlaps between stress adaptation and virulence. In *Advances in Applied Microbiology*; Elsevier Masson SAS: Amsterdam, The Netherlands, 2008; Volume 65, pp. 115–140.
157. Begley, M.; Sleator, R.D.; Gahan, C.G.; Hill, C. Contribution of three bile-associated loci, *bsh*, *pva*, and *btlB*, to gastrointestinal persistence and bile tolerance of *Listeria monocytogenes*. *Infect. Immun.* **2005**, *73*, 894–904. [[CrossRef](#)]
158. Sleator, R.D.; Wemekamp-Kamphuis, H.H.; Gahan, C.G.; Abee, T.; Hill, C. A PrfA-regulated bile exclusion system (BilE) is a novel virulence factor in *Listeria monocytogenes*. *Mol. Microbiol.* **2005**, *55*, 1183–1195. [[CrossRef](#)] [[PubMed](#)]
159. Wiedmann, M.; Arvik, T.J.; Hurley, R.J.; Boor, K.J. General stress transcription factor σ_B and its role in acid tolerance and virulence of *Listeria monocytogenes*. *J. Bacteriol.* **1998**, *180*, 3650–3656. [[CrossRef](#)] [[PubMed](#)]
160. Sue, D.; Fink, D.; Wiedmann, M.; Boor, K.J. σ_B -dependent gene induction and expression in *Listeria monocytogenes* during osmotic and acid stress conditions simulating the intestinal environment. *Microbiology* **2004**, *150*, 3843–3855. [[CrossRef](#)] [[PubMed](#)]
161. Cetin, M.S.; Zhang, C.; Hutkins, R.W.; Benson, A.K. Regulation of transcription of compatible solute transporters by the general stress sigma factor, σ_B , in *Listeria monocytogenes*. *J. Bacteriol.* **2004**, *186*, 794–802. [[CrossRef](#)]
162. Wemekamp-Kamphuis, H.H.; Wouters, J.A.; de Leeuw, P.P.; Hain, T.; Chakraborty, T.; Abee, T. Identification of sigma factor σ_B -controlled genes and their impact on acid stress, high hydrostatic pressure, and freeze survival in *Listeria monocytogenes* EGD-e. *Appl. Environ. Microbiol.* **2004**, *70*, 3457–3466. [[CrossRef](#)] [[PubMed](#)]

163. Lee, J.H.; Choi, C.W.; Lee, T.; Kim, S.I.; Lee, J.C.; Shin, J.H. Transcription factor σ B plays an important role in the production of extracellular membrane-derived vesicles in *Listeria monocytogenes*. *PLoS ONE* **2013**, *8*, e73196. [[CrossRef](#)] [[PubMed](#)]
164. Mujahid, S.; Orsi, R.H.; Vangay, P.; Boor, K.J.; Wiedmann, M. Refinement of the *Listeria monocytogenes* σ B regulon through quantitative proteomic analysis. *Microbiology* **2013**, *159*, 1109–1119. [[CrossRef](#)]
165. Abram, F.; Starr, E.; Karatzas, K.A.G.; Matlawska-Wasowska, K.; Boyd, A.; Wiedmann, M.; Boor, K.J.; Connally, D.; O'Byrne, C.P. Identification of components of the sigma B regulon in *Listeria monocytogenes* that contribute to acid and salt tolerance. *Appl. Environ. Microbiol.* **2008**, *74*, 6848–6858. [[CrossRef](#)] [[PubMed](#)]
166. Chaturongakul, S.; Boor, K.J. σ B activation under environmental and energy stress conditions in *Listeria monocytogenes*. *Appl. Environ. Microbiol.* **2006**, *72*, 5197–5203. [[CrossRef](#)] [[PubMed](#)]
167. Ferreira, A.; O'Byrne, C.P.; Boor, K.J. Role of σ B in heat, ethanol, acid, and oxidative stress resistance and during carbon starvation in *Listeria monocytogenes*. *Appl. Environ. Microbiol.* **2001**, *67*, 4454–4457. [[CrossRef](#)]
168. Garner, M.R.; Njaa, B.L.; Wiedmann, M.; Boor, K.J. Sigma B contributes to *Listeria monocytogenes* gastrointestinal infection but not to systemic spread in the guinea pig infection model. *Infect. Immun.* **2006**, *74*, 876–886. [[CrossRef](#)]
169. Guldimann, C.; Boor, K.J.; Wiedmann, M.; Guariglia-Oropeza, V. Resilience in the face of uncertainty: Sigma factor B fine-tunes gene expression to support homeostasis in gram-positive bacteria. *Appl. Environ. Microbiol.* **2016**, *82*, 4456–4469. [[CrossRef](#)] [[PubMed](#)]
170. Dessaux, C.; Guerreiro, D.N.; Pucciarelli, M.G.; O'Byrne, C.P.; García-del Portillo, F. Impact of osmotic stress on the phosphorylation and subcellular location of *Listeria monocytogenes* stressosome proteins. *Sci. Rep.* **2020**, *10*, 20837. [[CrossRef](#)]
171. Chaturongakul, S.; Boor, K.J. RsbT and RsbV contribute to σ B-dependent survival under environmental, energy, and intracellular stress conditions in *Listeria monocytogenes*. *Appl. Environ. Microbiol.* **2004**, *70*, 5349–5356. [[CrossRef](#)]
172. Freitag, N.E.; Port, G.C.; Miner, M.D. *Listeria monocytogenes*: From saprophyte to intracellular pathogen. *Nat. Rev. Microbiol.* **2009**, *7*, 623. [[CrossRef](#)]
173. Freitag, N.E.; Rong, L.; Portnoy, D.A. Regulation of the *prfA* transcriptional activator of *Listeria monocytogenes*: Multiple promoter elements contribute to intracellular growth and cell-to-cell spread. *Infect. Immun.* **1993**, *61*, 2537–2544. [[CrossRef](#)] [[PubMed](#)]
174. Gray, M.J.; Freitag, N.E.; Boor, K.J. How the bacterial pathogen *Listeria monocytogenes* mediates the switch from environmental Dr. Jekyll to pathogenic Mr. Hyde. *Infect. Immun.* **2006**, *74*, 2505–2512. [[CrossRef](#)]
175. Miner, M.D.; Port, G.C.; Freitag, N.E. Regulation of *Listeria monocytogenes* virulence genes. In *Listeria monocytogenes: Pathogenesis and Host Response*; Goldfine, H., Shen, H., Eds.; Springer Science+Business Media, LLC: Berlin, Germany, 2007; pp. 139–158.
176. Bruno, J.C.; Freitag, N.E. Constitutive activation of PrfA tilts the balance of *Listeria monocytogenes* fitness towards life within the host versus environmental survival. *PLoS ONE* **2010**, *5*, e15138. [[CrossRef](#)] [[PubMed](#)]
177. Biswas, R.; Sonenshein, A.L.; Belitsky, B.R. Genome-wide identification of *Listeria monocytogenes* CodY-binding sites. *Mol. Microbiol.* **2020**, *113*, 841–858. [[CrossRef](#)]
178. Lobel, L.; Sigal, N.; Borovok, I.; Belitsky, B.R.; Sonenshein, A.L.; Herskovits, A.A. The metabolic regulator CodY links *Listeria monocytogenes* metabolism to virulence by directly activating the virulence regulatory gene *prfA*. *Mol. Microbiol.* **2015**, *95*, 624–644. [[CrossRef](#)] [[PubMed](#)]
179. Lobel, L.; Herskovits, A.A. Systems level analyses reveal multiple regulatory activities of CodY controlling metabolism, motility and virulence in *Listeria monocytogenes*. *PLoS Genet.* **2016**, *12*, e1005870. [[CrossRef](#)]
180. Lobel, L.; Sigal, N.; Borovok, I.; Rupp, E.; Herskovits, A. Integrative genomic analysis identifies isoleucine and CodY as regulators of *Listeria monocytogenes* virulence. *PLoS Genet.* **2012**, *8*, e1002887. [[CrossRef](#)]
181. Chico-Calero, I.; Suárez, M.; González-Zorn, B.; Scotti, M.; Slaghuis, J.; Goebel, W.; Vázquez-Boland, J.A.; European Listeria Genome Consortium. Hpt, a bacterial homolog of the microsomal glucose-6-phosphate translocase, mediates rapid intracellular proliferation in *Listeria*. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 431–436. [[CrossRef](#)] [[PubMed](#)]
182. Vega, Y.; Rauch, M.; Banfield, M.J.; Ermolaeva, S.; Scotti, M.; Goebel, W.; Vázquez-Boland, J.A. New *Listeria monocytogenes* *prfA** mutants, transcriptional properties of PrfA* proteins and structure-function of the virulence regulator PrfA. *Mol. Microbiol.* **2004**, *52*, 1553–1565. [[CrossRef](#)] [[PubMed](#)]
183. Xayarath, B.; Smart, J.I.; Mueller, K.J.; Freitag, N.E. A novel C-terminal mutation resulting in constitutive activation of the *Listeria monocytogenes* central virulence regulatory factor PrfA. *Microbiology* **2011**, *157*, 3138–3149. [[CrossRef](#)]
184. Oropeza, V.G.; Orsi, R.H.; Guldimann, C.; Wiedmann, M.; Boor, K.J. The *Listeria monocytogenes* bile stimulon under acidic conditions is characterized by strain-specific patterns and the upregulation of motility, cell wall modification functions, and the PrfA regulon. *Front. Microbiol.* **2018**, *9*, 120. [[CrossRef](#)]
185. Eshwar, A.K.; Guldimann, C.; Oevermann, A.; Tasara, T. Cold-shock domain family proteins (Csps) are involved in regulation of virulence, cellular aggregation, and flagella-based motility in *Listeria monocytogenes*. *Front. Cell. Infect. Microbiol.* **2017**, *7*, 453. [[CrossRef](#)]
186. Wałęcka, E.; Molenda, J.; Karpíšková, R.; Bania, J. Effect of osmotic stress and culture density on invasiveness of *Listeria monocytogenes* strains. *Int. J. Food. Microbiol.* **2011**, *144*, 440–445. [[CrossRef](#)] [[PubMed](#)]
187. Kim, H.; Marquis, H.; Boor, K.J. σ B contributes to *Listeria monocytogenes* invasion by controlling expression of *inlA* and *inlB*. *Microbiology* **2005**, *151*, 3215–3222. [[CrossRef](#)] [[PubMed](#)]

188. Dussurget, O.; Cabanes, D.; Dehoux, P.; Lecuit, M.; Buchrieser, C.; Glaser, P.; Cossart, P. European *Listeria* Genome Consortium *Listeria monocytogenes* bile salt hydrolase is a PrfA-regulated virulence factor involved in the intestinal and hepatic phases of listeriosis. *Mol. Microbiol.* **2002**, *45*, 1095–1106. [[PubMed](#)]
189. Tiensuu, T.; Andersson, C.; Rydén, P.; Johansson, J. Cycles of light and dark co-ordinate reversible colony differentiation in *Listeria monocytogenes*. *Mol. Microbiol.* **2013**, *87*, 909–924. [[CrossRef](#)] [[PubMed](#)]
190. Shetron-Rama, L.M.; Marquis, H.; Bouwer, H.G.A.; Freitag, N.E. Intracellular induction of *Listeria monocytogenes actA* expression. *Infect. Immun.* **2002**, *70*, 1087–1096. [[CrossRef](#)] [[PubMed](#)]
191. Ollinger, J.; Bowen, B.; Wiedmann, M.; Boor, K.J.; Bergholz, T.M. *Listeria monocytogenes* σ B modulates PrfA-mediated virulence factor expression. *Infect. Immun.* **2009**, *77*, 2113–2124. [[CrossRef](#)] [[PubMed](#)]
192. Rauch, M.; Luo, Q.; Müller-Altrock, S.; Goebel, W. SigB-dependent in vitro transcription of *prfA* and some newly identified genes of *Listeria monocytogenes* whose expression is affected by PrfA in vivo. *J. Bacteriol.* **2005**, *187*, 800–804. [[CrossRef](#)]
193. Lam, O.; Wheeler, J.; Tang, C.M. Thermal control of virulence factors in bacteria: A hot topic. *Virulence* **2014**, *5*, 852–862. [[CrossRef](#)] [[PubMed](#)]
194. Loh, E.; Righetti, F.; Eichner, H.; Twittenhoff, C.; Narberhaus, F. RNA thermometers in bacterial pathogens. *Microbiol. Spectr.* **2018**, *6*. [[CrossRef](#)] [[PubMed](#)]
195. Loh, E.; Memarpour, F.; Vaitkevicius, K.; Kallipolitis, B.H.; Johansson, J.; Sondén, B. An unstructured 5'-coding region of the *prfA* mRNA is required for efficient translation. *Nucleic Acids Res.* **2012**, *40*, 1818–1827. [[CrossRef](#)] [[PubMed](#)]
196. Dorey, A.; Marinho, C.; Piveteau, P.; O'byrne, C. Role and regulation of the stress activated sigma factor sigma B (σ B) in the saprophytic and host-associated life stages of *Listeria monocytogenes*. In *Advances in Applied Microbiology*, 1st ed.; Gadd, G.M., Sariaslani, S., Eds.; Elsevier Inc.: Amsterdam, The Netherlands, 2019; pp. 1–48.
197. Bennett, H.J.; Pearce, D.M.; Glenn, S.; Taylor, C.M.; Kuhn, M.; Sonenshein, A.L.; Andrew, P.W.; Roberts, I.S. Characterization of *relA* and *codY* mutants of *Listeria monocytogenes*: Identification of the CodY regulon and its role in virulence. *Mol. Microbiol.* **2007**, *63*, 1453–1467. [[CrossRef](#)] [[PubMed](#)]
198. Reniere, M.; Whiteley, A.; Hamilton, K.L.; John, S.M.; Lauer, P.; Brennan, R.; Portnoy, D.A. Glutathione activates virulence gene expression of an intracellular pathogen. *Nature* **2015**, *517*, 170–173. [[CrossRef](#)]
199. Hall, M.; Grundström, C.; Begum, A.; Lindberg, M.J.; Sauer, U.H.; Almqvist, F.; Johansson, J.; Sauer-Eriksson, A.E. Structural basis for glutathione-mediated activation of the virulence regulatory protein PrfA in *Listeria*. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 14733–14738. [[CrossRef](#)] [[PubMed](#)]
200. Gopal, S.; Borovok, I.; Ofer, A.; Yanku, M.; Cohen, G.; Goebel, W.; Kreft, J.; Aharonowitz, Y. A multidomain fusion protein in *Listeria monocytogenes* catalyzes the two primary activities for glutathione biosynthesis. *J. Bacteriol.* **2005**, *187*, 3839–3847. [[CrossRef](#)]
201. Schärer, K.; Stephan, R.; Tasara, T. Cold shock proteins contribute to the regulation of listeriolysin O production in *Listeria monocytogenes*. *Foodborne Pathog. Dis.* **2013**, *10*, 1023–1029. [[CrossRef](#)]
202. Cheng, Y.; Siletzky, R.M.; Kathariou, S. Genomic Divisions/Lineages, Epidemic Clones, and Population Structure. In *Handbook of Listeria monocytogenes*; Liu, D., Ed.; CRC Press: Boca Raton, FL, USA, 2008; pp. 337–358.
203. Orsi, R.H.; den Bakker, H.C.; Wiedmann, M. *Listeria monocytogenes* lineages: Genomics, evolution, ecology, and phenotypic characteristics. *Int. J. Med. Microbiol.* **2011**, *301*, 79–96. [[CrossRef](#)] [[PubMed](#)]
204. Moura, A.; Criscuolo, A.; Pouseele, H.; Maury, M.M.; Leclercq, A.; Tarr, C.; Björkman, J.T.; Dallman, T.; Reimer, A.; Enouf, V.; et al. Whole genome-based population biology and epidemiological surveillance of *Listeria monocytogenes*. *Nat. Microbiol.* **2016**, *2*, 16185. [[CrossRef](#)] [[PubMed](#)]
205. Haase, J.K.; Didelot, X.; Lecuit, M.; Korkeala, H. *L. monocytogenes* MSLT Study Group; Achtman, M. The ubiquitous nature of *Listeria monocytogenes* clones: A large-scale Multilocus Sequence Typing study. *Environ. Microbiol.* **2014**, *16*, 405–416. [[CrossRef](#)]
206. Doijad, S.; Weigel, M.; Barbuddhe, S.; Blom, J.; Goesmann, A.; Hain, T.; Chakraborty, T. Phylogenomic grouping of *Listeria monocytogenes*. *Can. J. Microbiol.* **2015**, *61*, 637–646. [[CrossRef](#)]
207. Schiavano, G.F.; Ateba, C.N.; Petruzzelli, A.; Mele, V.; Amagliani, G.; Guidi, F.; De Santi, M.; Pomilio, F.; Blasi, G.; Gattuso, A.; et al. Whole-genome sequencing characterization of virulence profiles of *Listeria monocytogenes* food and human isolates and in vitro adhesion/invasion assessment. *Microorganisms* **2022**, *10*, 62. [[CrossRef](#)] [[PubMed](#)]
208. Deng, X.; Phillippy, A.M.; Li, Z.; Salzberg, S.L.; Zhang, W. Probing the pan-genome of *Listeria monocytogenes*: New insights into intraspecific niche expansion and genomic diversification. *BMC Genom.* **2010**, *11*, 500. [[CrossRef](#)]
209. Maury, M.M.; Tsai, Y.H.; Charlier, C.; Touchon, M.; Chenal-Francois, V.; Leclercq, A.; Criscuolo, A.; Gaultier, C.; Roussel, S.; Brisabois, A.; et al. Uncovering *Listeria monocytogenes* hypervirulence by harnessing its biodiversity. *Nat. Genet.* **2016**, *48*, 308. [[CrossRef](#)] [[PubMed](#)]
210. Vázquez-Boland, J.A.; Wagner, M.; Scortti, M. Why are some *Listeria monocytogenes* genotypes more likely to cause invasive (brain, placental) infection? *mBio* **2020**, *11*, e03126-20. [[CrossRef](#)]
211. Lee, S.; Chen, Y.; Gorski, L.; Ward, T.J.; Osborne, J.; Kathariou, S. *Listeria monocytogenes* source distribution analysis indicates regional heterogeneity and ecological niche preference among serotype 4b clones. *mBio* **2018**, *9*, e00396-18. [[CrossRef](#)]
212. da Silva, M.F.; Ferreira, V.; Magalhães, R.; Almeida, G.; Alves, A.; Teixeira, P. Detection of premature stop codons leading to truncated internalin A among food and clinical strains of *Listeria monocytogenes*. *Food Microbiol.* **2017**, *63*, 6–11. [[CrossRef](#)]

213. Nightingale, K.K.; Ivy, R.A.; Ho, A.J.; Fortes, E.D.; Njaa, B.L.; Peters, R.M.; Wiedmann, M. *inlA* premature stop codons are common among *Listeria monocytogenes* isolates from foods and yield virulence-attenuated strains that confer protection against fully virulent strains. *Appl. Environ. Microbiol.* **2008**, *74*, 6570–6583. [[CrossRef](#)] [[PubMed](#)]
214. Van Stelten, A.; Simpson, J.M.; Ward, T.J.; Nightingale, K.K. Revelation by single-nucleotide polymorphism genotyping that mutations leading to a premature stop codon in *inlA* are common among *Listeria monocytogenes* isolates from ready-to-eat foods but not human listeriosis cases. *Appl. Environ. Microbiol.* **2010**, *76*, 2783–2790. [[CrossRef](#)] [[PubMed](#)]
215. Cotter, P.D.; Draper, L.A.; Lawton, E.M.; Daly, K.M.; Groeger, D.S.; Casey, P.G.; Ross, R.P.; Hill, C. Listeriolysin S, a novel peptide haemolysin associated with a subset of lineage I *Listeria monocytogenes*. *PLoS Pathog.* **2008**, *4*, e1000144. [[CrossRef](#)]
216. Quereda, J.J.; Meza-Torres, J.; Cossart, P.; Pizarro-Cerdá, J. Listeriolysin S: A bacteriocin from epidemic *Listeria monocytogenes* strains that targets the gut microbiota. *Gut Microbes* **2017**, *8*, 384–391. [[CrossRef](#)] [[PubMed](#)]
217. Bergholz, T.M.; den Bakker, H.C.; Fortes, E.D.; Boor, K.J.; Wiedmann, M. Salt stress phenotypes in *Listeria monocytogenes* vary by genetic lineage and temperature. *Foodborne Pathog. Dis.* **2010**, *7*, 1537–1549. [[CrossRef](#)] [[PubMed](#)]
218. Horlbog, J.A.; Kent, D.; Stephan, R.; Guldemann, C. Surviving host- and food relevant stresses: Phenotype of *L. monocytogenes* strains isolated from food and clinical sources. *Nat. Sci. Rep.* **2018**, *8*, 12931. [[CrossRef](#)]
219. Pirone-Davies, C.; Chen, Y.; Pightling, A.; Ryan, G.; Wang, Y.; Yao, K.; Hoffmann, M.; Allard, M.W. Genes significantly associated with lineage II food isolates of *Listeria monocytogenes*. *BMC Genom.* **2018**, *19*, 708. [[CrossRef](#)]
220. Naditz, A.L.; Dzieciol, M.; Wagner, M.; Schmitz-Esser, S. Plasmids contribute to food processing environment-associated stress survival in three *Listeria monocytogenes* ST121, ST8, and ST5 strains. *Int. J. Food Microbiol.* **2019**, *299*, 39–46. [[CrossRef](#)]
221. Korsak, D.; Chmielowska, C.; Szuplewska, M.; Bartosik, D. Prevalence of plasmid-borne benzalkonium chloride resistance cassette *bcrABC* and cadmium resistance *cadA* genes in nonpathogenic *Listeria* spp. isolated from food and food-processing environments. *Int. J. Food Microbiol.* **2019**, *290*, 247–253. [[CrossRef](#)] [[PubMed](#)]
222. Gelbicova, T.; Florianova, M.; Hluchanova, L.; Kalova, A.; Korena, K.; Strakova, N.; Karpiskova, R. Comparative analysis of genetic determinants encoding cadmium, arsenic, and benzalkonium chloride resistance in *Listeria monocytogenes* of human, food, and environmental origin. *Front. Microbiol.* **2021**, *11*, 599882. [[CrossRef](#)]
223. Cerutti, F.; Mallet, L.; Painset, A.; Hoede, C.; Moisan, A.; Bécavin, C.; Duval, M.; Dussurget, O.; Cossart, P.; Gaspin, C.; et al. Unraveling the evolution and coevolution of small regulatory RNAs and coding genes in *Listeria*. *BMC Genom.* **2017**, *18*, 882. [[CrossRef](#)]