Review on Stress Tolerance in Campylobacter jejuni

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Campylobacter spp. are the leading global cause of bacterial colon infections in humans. Enteropathogens are subjected to several stress conditions in the host colon, food complexes, and the environment. Species of the genus Campylobacter, in collective interactions with certain enteropathogens, can manage and survive such stress conditions. The stress-adaptation mechanisms of Campylobacter spp. diverge from other enteropathogenic bacteria, such as Escherichia coli, Salmonella enterica serovar Typhi, S. enterica ser. Paratyphi, S. enterica ser. Typhimurium, and species of the genera Klebsiella and Shigella. This review summarizes the different mechanisms of various stress-adaptive factors on the basis of species diversity in Campylobacter, including their response to various stress conditions that enhance their ability to survive on different types of food and in adverse environmental conditions. Understanding how these stress adaptation mechanisms in Campylobacter, and other enteric bacteria, are used to overcome various challenging environments facilitates the fight against resistance mechanisms in Campylobacter spp., and aids the development of novel therapeutics to control Campylobacter in both veterinary and human populations.

Keywords: Campylobacter, stress, resistance mechanisms, stress adaptation, enteric bacteria
INTRODUCTION

Campylobacter are a Gram-negative, slender, microaerophilic bacteria with a spiral or curved shape (0.2–0.8 mm × 0.5–5 mm). All species of the genus Campylobacter, with the exception of Campylobacter gracilis (nonmotile) and Campylobacter showae (peritrichous flagella), have a single, polar, unsheathed flagellum on one or both sides of the cell. Infection with Campylobacter in humans predominantly occurs through handling and ingestion of Campylobacter-contaminated raw or undercooked meat, raw milk, tap water, chicken salad, and various chicken-containing dishes (Zhao et al., 2003; Jang et al., 2007; Pedersen et al., 2018; Ovesen et al., 2019; The et al., 2019) as illustrated in Figure 1. Most Campylobacter infections involve a mild and self-limiting gastroenteritis, with one to three days of fever and vomiting, followed by abdominal pain with watery or bloody diarrhea for three to seven days (Negretti et al., 2019).

The species Campylobacter jejuni is a zoonotic pathogen that frequently causes acute gastrointestinal infections in humans when undercooked or raw meat or other products are consumed. Fever, vomiting, abdominal pain, and diarrhea are the prevalent symptoms of campylobacteriosis (Altekruse et al., 1999; Gaynor et al., 2005). In some cases, C. jejuni is associated with bacteremia and several post-infectious complications in humans, including immunoreactions and chronic and life-threatening paralysis, such as Guillain–Barre syndrome (GBS) and Miller Fisher syndrome (MFS) (Humphrey et al., 2007; EFSA, 2011).

C. jejuni possesses novel regulatory factors for stress resistance that enable the organism to cause foodborne infections (CDC, 2013). In most pathogens, sigma factor RpoS plays a key role in the stress-resistance mechanisms, but this factor has been reported to be absent in C. jejuni (Allen et al., 2018; Cain et al., 2019). Campylobacter is a foodborne pathogen with high incidence with norovirus, enteropathogenic Escherichia coli, and Salmonella in South Korea (Kim et al., 2017; Wang et al., 2020).

The prevalence of thermophilic Campylobacter for poultry is C. jejuni (6.3%), C. upsaliensis (5.9%), and C. coli (0.7%). Globally 20.9% C. jejuni are resistant to (fluoro)quinolones. Poultry
become colonized shortly after birth; commercial broilers are often particularly colonized with *C. jejuni* (EFSA, 2010), the major transmission of *C. jejuni* occurs in small intestinal crypts of poultry within 24 hours (Coward et al., 2008). *Campylobacter* can reach densities as high as $1 \times 10^8$ colony-forming units (CFU/g) in the infected bird’s intestinal mucosa are asymptomatic (Meade et al., 2009). *C. jejuni* spreads to a small intestine of the gastrointestinal tract, sometimes asymptptomatically, after human consumption. The onset of illness is affected by the immune status of the host and the virulence of the *Campylobacter* strain.

The pathogenesis of *C. jejuni* foodborne illness involves adhesions, gut-wall invasion, colonization, and ultimately the release of toxins (Bang et al., 2003; Bolton, 2015; Pedersen et al., 2018). Motility of this pathogen is a key factor influencing colonization and survival in the acidic gut environment (Guerry, 2007; Mehat et al., 2018; Negretti et al., 2019). Flagella-oriented genes such as *flaA* and *flaB*, and *flF*, *flM*, and *flY* are associated with motility-engaged *C. jejuni* (Nachamkin et al., 1993; Wassenaar et al., 1993; Carrillo et al., 2004; Sommerlad and Hendrixson, 2007; Lerssethakarn et al., 2011). Some Gram-negative bacteria secrete a cytotoxic distending toxin (CDT) heat-labile exotoxin and able to induce the distension and death of eukaryotic cells, and this has been demonstrated in *Campylobacter* (Bolton, 2015; Scuron et al., 2016; Pedersen et al., 2018; El-Tawab et al., 2019), which synthesizes this toxin using the genes *cdtA*, *cdtB*, and *cdtC* (Linton et al., 2000; Asakura et al., 2007; Wieczorek et al., 2018). Motility, adherence, invasion, and toxin production are required for cell lysis (Bang et al., 2003). The flagellar guidance of the motility scheme and a chemosensory mechanism that activates flagellar motion result in transmission from the environment to the small bowel (O’Sullivan et al., 2018). *Campylobacter* has extraordinary motility, particularly in gelatinous or viscous material, as indicated by its single or bipolar flagella and helical filamentous structures. The polar flagellum delivers driving torque and rotating metabolic signals, while corkscrew rotation is possible due to the helical form (Ferrero and Lee, 1988). Mucins and glycoproteins, the predominant components of mucus, are the primary chemical attractants during propagation (Hugdahl et al., 1988; Wadhams and Armitage, 2004; Wuichet et al., 2007; Ellström et al., 2016). Iron acquisition also plays a key role in infection with *Campylobacter* (Baillon et al., 1999; Bang et al., 2003; Eucker and Konkel, 2012).

The purpose of this review was to examine the mechanisms that enable *Campylobacter* spp. to survive outside the host environment and remain a threat to public health. A summary of specific survival-based resistance genes is also provided. This information helps identify future pathways to eradicate and control outbreaks of *C. jejuni*.

**GENERAL SURVIVAL MECHANISMS IN ENTERIC BACTERIA: MICRO-ORGANISM CROSS-PROTECTION**

An extraordinary characteristic of bacteria is their ability to tolerate extreme environmental conditions or stressors. They
not only tolerate ecological stress, but also adapt to different situations such as pressure, temperature, acidity, ultraviolet radiation, dehydration, susceptibility to antibiotics, and salinity. These characteristics raise some questions. Why and how do microbes in these environments survive? What biological mechanisms can we observe from these unique lifestyles? How can we use our understanding or resources to address these conditions, such as pH or temperature, to enhance or slow the growth of microbes?

Micro-organisms commonly face stress or shock during food processing (Ma et al., 2014). Microbes can survive in stressful or adverse environments, and can then tolerate other comparable stressors following the initial stress conditions (Isohanni et al., 2013). Cross-protection capabilities have been identified in *Salmonella* spp., *E. coli*, *Listeria monocytogenes*, and *Cronobacter sakazakii* (Kim et al., 2012; Spector and Kenyon, 2012; Lapierre et al., 2016; Wieczorek et al., 2018). For *C. jejuni*, a higher resistance to stress was observed following exposure to previous stressful environments. *C. jejuni* displayed tolerance or resistance to acid due to acquaintance with acid-aerobic, acidic, and nutrition-deprived stress (Oh et al., 2017), as well as showing oxidative stress cross-protection resulting from acid disturbance (Xu et al., 2019). However, Isohanni and Lyhs (Isohanni et al., 2013) stated that after exposure to heat and cold, *C. jejuni* did not have any cross-protection capacity, as shown in Figure 2.

Evidence indicates that antimicrobial agents are not used or are used incorrectly for the production of resistance *Campylobacter* spp. (Pedersen et al., 2018). Patients generally recover from campylobacteriosis without antimicrobial therapy, with treatment based on electrolyte substitution and rehydration. Severe cases can be managed with antibiotics such as tetracycline and macrolides (fluoro) or quinolones, but increases in antibiotic resistance in *C. jejuni* and *C. coli* has jeopardized the effectiveness of these therapeutics (Alfredson and Korolik, 2007; Bolinger et al., 2018).

Early in the food supply chain, *C. jejuni* is exposed to oxidative and desiccation stresses. *Campylobacter* are especially susceptible to the former as a processing technique (Humphrey et al., 1995), and in slaughter facilities, survival of *Campylobacter* in pig, and chicken meat decreases significantly by air-chill-drying the carcass surface (Oosterom et al., 1983). No comparable technique is used during the processing of poultry, and the chilling method initiates the formation of a moist surface that helps bacteria thrive (Butzler and Oosterom, 1991). Due to incomplete oxygen reduction, aerobic respiration generates reactive oxygen species (ROS), including superoxide anions (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$), which can lead to the formation of the extremely poisonous hydroxyl radical (HO). *Campylobacter* in the chicken or human body can also be subjected to H$_2$O$_2$ or O$_2$ by the immune system to kill the microbes (Melo et al., 2019). The range of enzymes such as catalase, glutathione, cytochrome, peroxidases, peroxiredoxin alkyl hydroperoxide reductase, superoxide dismutase, and other peroxiredoxins are activated in *Campylobacter* exposed to ROS and these then facilitate long-term aerobic adaptation of the bacteria (Storz and Imlay, 1999) to facilitate long-term aerobic adaptation (Jones et al., 1993; Klancnik et al., 2009). *C. jejuni* has one catalase, KatA, which supports this process when
the cytoplasmic level of \( \text{H}_2\text{O}_2 \) is high (Bingham-Ramos and Hendrixson, 2008; Melo et al., 2019).

Thermophilic species of \textit{Campylobacter}, like \textit{C. jejuni}, multiply at 37 to 42°C and are unable to grow at temperatures below 30°C (optimal growth is at 41.5°C). At different stages of food processing, \textit{Campylobacter} are exposed to chilled (0–4°C) and elevated (>37–42°C) temperatures. Evidence has shown that the response of \textit{Campylobacter} to colder conditions (Hazeleger et al., 1998; Park, 2002) results in the slowest growth at 30°C. Low temperatures, freezing, and thawing impact different kinds of wastewater (particularly those concerning public health) and their long-term survival of enteric microbes (Zhang et al., 2009; Dasti et al., 2010; Hazeleger et al., 1998). Differences in at least 15 distinct genes were recorded between bacterial-cell and human-body temperatures of 37–42°C, which is within the range of chicken-body temperatures. Around 48.1% of \textit{C. jejuni} isolates showed resistance to tetracycline, and subsequent resistance to nalidixic acid (5.5%), ciprofloxacin (5.5%), azithromycin (1.78%), and erythromycin (1.78%) (Navrava-Bravo et al., 2017). Dasti et al. (2010) reported ciprofloxacin resistance ranging from 4 \( \mu \text{g} \) to 32 \( \mu \text{g}/\text{ml} \) for the minimal inhibitory concentration. Most ciprofloxacin-resistant strains were divided into three major clonal complexes (ST-21, 48, and 353) by multilocus assessment, whereas both antibiotic-resistant strains were uniquely grouped into ST-45.

### OTHER GENERAL SURVIVAL MECHANISMS

The food matrix is one environmental factor that can influence micro-organism survival in the food system (all processes of production, processing, transport, and consumption) (de Oliveira et al., 2019; Farfán et al., 2019). After exposure to stress in the food system, expression of virulence and survival genes increased in \textit{Listeria monocytogenes} (Olesen et al., 2009; Farfán et al., 2019). Day and Hammack (2019), reported enhanced gene expression under stress tolerance in \textit{L. monocytogenes} in processed foods like meat and sausage juices compared with a laboratory setting. In contrast, stress-tolerance genes of \textit{Lactobacillus sakei} were decreased in meat products (Prechtl et al., 2018), chicken meat and juice (Birk et al., 2004). Meat exudate, such as that from poultry meat, contains enzymes, myogens, myoglobin lacid, and amino acids (Wang et al., 2013). ‘Chicken juice’ can be used as a food-based model system for investigation of microbial survivability. Birk et al. (2004) recommended using the system to enhance understanding of \textit{C. jejuni} viability on poultry products. \textit{C. jejuni} survived longer in chicken juice (due to increased biofilm formation) stored at 5°C and 10°C (Brown et al., 2014). Ligowska et al. (2011) reported that expression of the gene \textit{luxS} was increased in \textit{C. jejuni} cultured in chilled poultry-meat juice. This highly conserved gene encodes the enzyme LuxS (S-ribosylhomocysteine lyase), which forms part of a quorum sensing system with autoinducer-2 (AI-2) and regulates gene expression. Differences in the recovery and identification of \textit{Campylobacter} spp. between meat exudate and carcass rinse sampling methods in poultry have been demonstrated (Simmons et al., 2008; Duffy, 2019), as shown in Figure 3.

Previous research has shown that microbes form biofilms during food processing, such as in meat exudate conditions. Species of the genus \textit{Salmonella} created a biofilm on the surface of stainless steel when cultured in laboratory media or meat exudate (Wang et al., 2013). Differences in the shape and cell density of mature biofilms were observed between food processing and laboratory environments. Longo and Spano (2019) reported the formation of biofilm in \textit{L. monocytogenes} and species of the genera \textit{Pseudomonas} and \textit{Staphylococcus} on meat-treated surfaces, such as polyvinyl chloride, polyurethane, and steel. \textit{C. jejuni} was more prone to forming biofilms in chicken juice than in a laboratory environment due to high nutrient availability (Brown et al., 2014). Thus, processed foods that contain many macronutrients are easily contaminated by microbes; these foods include the meat juice of chicken and beef, milk protein, and dairy products (Kusumaningrum et al., 2003; Healy et al., 2010).

### VIABLE BUT NON-CULTURABLE (VBNC) STATE

Some microbes can endure unfavorable environments, such as nutrient deprivation, desiccation, inadequate pH, and temperature changes (Blanco-Lizarazo et al., 2018; Jin and Riedel-Kruse, 2018). Few microbes are capable of living in these unfavorable environments, but some organisms may enter a VBNC state for subsistence. Microbes in the VBNC state are unable to multiply, and their morphology is transformed into a coccoid shape (Poursina et al., 2018; Jin and Riedel-Kruse, 2018). Bacteria decrease their metabolism in the VBNC state but may retain the virulence capacity to infect a host and cause disease (Oliver, 2010; Fakruddin et al., 2013; Poursina et al., 2018). The VBNC state has been found in several micro-organisms, such as \textit{C. jejuni}, \textit{V. parahaemolyticus}, \textit{Salmonella} ser. Typhi, and \textit{Helicobacter pylori} (Azevedo et al., 2007; Zeng et al., 2013; Otigbu et al., 2018; Yoon and Lee, 2020). In an unfavorable environment, \textit{C. jejuni} can survive by using the VBNC tactic (Gangaiah et al., 2010; Zeng et al., 2013; Otigbu et al., 2018; Yoon and Lee, 2020). \textit{C. jejuni} entered the VBNC state when cultured for 18–28 days at 4°C (Jones et al., 1991). Magajna and Schraft (2015) studied the VBNC status of planktonic cells and biofilm cells at 4°C and found that biofilm cells converted to VBNC status quicker than planktonic cells in nutritionally deprived and hostile-temperature environments. The VBNC form of \textit{C. jejuni} affects CadF expression at 4°C (Otigbu et al., 2018). CadF protein is one of the elements influencing microbial invasion. The VBNC form of \textit{Campylobacter} has been categorized based on reduced metabolism, augmented production of the degrading enzymes and substrates, and (Chaveerach et al., 2003; Upadhyay et al., 2019). Consequently, microbes can live for longer periods in hostile conditions (Kovacs et al., 2019).
ADAPTATION TO MAJOR ENVIRONMENTAL STRESSES BY CAMPYLOBACTER SPP.

Adaptation by *Campylobacter* spp. to various stresses such as acidic environment, salt tolerance, thermostolerance (heat and cold), UV stress, osmotolerance, desiccation, biofilm formation, and antibiotic resistance, are explained in detail in Table 1.

**Genes Involved in Stress Sensing/Adaptation**

Acid-tolerance mechanisms: The adaptive tolerance response (ATR) was identified as the initiator of cross-protection for the survival of microbes under various stressful or unfavorable conditions (Oh et al., 2015), and was also found in foodborne pathogens (Li et al., 2018; Cariri et al., 2019; Mayton et al., 2019). Murphy et al. (2003) discovered an ATR in *C. jejuni* and a comparable result in the initiation of ATR was observed between stress-exposed and nonexposed organisms when the organism at the mid-exponential stage (8 h) was unable to start an ATR under air- and acidic-stress conditions. Conversely, stationary-phase (48 h) organisms could initiate ATR at pH 4.5 under air and acidic status compared to nonexposed organisms. They displayed acidic cross-protection, which initiated ATR under oxygen or air status. In addition, the ATR initiation of microbes at pH 4.5 varies according to the culture media; this might be due to the different nutrient compositions of the various culture media (Kovacs et al., 2019). *C. jejuni* demonstrated an ATR capacity at pH 4.5 when exposed to aerobic conditions with acidic and nutritional deprivation (Oh et al., 2017). Acidic stress initiated the upregulation of *perR* genes to counter oxidative disturbance.

Acid shock has a significant biological impact in situations of acidic pH and low (organic) acids. Fatty acids are carboxylic acids generated by fermentation, and include propionate, butyrate, and acetate (Luo et al., 2015; Eguchi and Utsumi, 2016). The fatty acids cause toxicity in their unloaded, protonated form because they may penetrate the plasma membrane, dissociate a proton, and create a lower intracellular pH.

An adaptive tolerance response to aerobic + acid conditions in *C. jejuni* (Oh et al., 2019) was shown to induce a global stress response mechanism (S.H Kim, unpublished data). An adaptive tolerance response (ATR) produced as a result of sub-chronic

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**FIGURE 3** | Summary of *C. jejuni* responses to stresses. The chromosome of *C. jejuni* NCTC11168 is represented by a black circle on which the location of genes, involved in different stress responses, are shown as colored lines. Genes are colored according to their role; gene names shaded in grey are involved in multiple stress responses.
stress adaptive response and offers protection against subsequent lethal stress exposure (Noreen, 2019). We have defined an ATR in C. jejuni previously. The mediation of acid and oxygen concentration, makes them to adopt improved survival mechanism against lethal pH (Taylor et al., 2017). De novo protein synthesis was necessary for the initiation of ATR in C. jejuni, which implies enhanced protein synthesis occurred during the induction phase. During the induction of an ATR to acid stress, analysis of protein expression profiles demonstrated a global cellular response (S.H Kim, unpublished data). Based on MALDI-TOF mass spectrometry different Protein expressed during induction of the ATR in C. jejuni, which revealed that the majority of proteins were involved in modification, repair and biosynthesis.

The ATR in C. jejuni has been shown to incorporate up-regulation of generic stress proteins involved in protein defense or breakdown, such as the heat-shock response based on universal chaperones DnaK and GroEL, which are among the

| Sr. No | Target Mechanism | Gene | Stress tolerant Gene | Reference |
|-------|------------------|------|----------------------|-----------|
| 1     | Nitric Oxide and Nitrosative Stress in Campylobacter jejuni and Campylobacter coli | nrfA | Nitrite reductase, formate-dependent | Mühlig et al., 2014; Evers et al., 2004; Pittman et al., 2007; Monk et al., 2008; Avila-Ramirez et al., 2013 |
| 2     | Heat shock efficiency | htrB | Promotes Azotobacter and Biotic Stress Tolerance in Transgenic Arabidopsis thaliana | Svensson et al., 2008; Poli et al., 2012 |
|       |                   | htrA | high-temperature requirement A (HtrA)-like protease and chaperones in the cell envelope, | Svensson et al., 2008 |
|       |                   | groES/groEL | Chaperonin | Laranjo and Oliveira, 2011 |
|       |                   | dnaK | Chaperonin | Gerth et al., 1998 |
|       |                   | ctpP | Two promoters; proteolytic component of the Clp or Ti protease | Völker et al., 1992 |
|       |                   | grpE | Nucleotide sequence of a Bacillus subtilis gene homologous to the grpE gene | |
|       |                   | dnaJ | Arabidopsis DnaJ (Hsp40) contributes to NaCl-stress tolerance | Zhiang et al., 2010 |
|       |                   | hslU | Proteomics Analysis of Drought Stress-Responsive Proteins | Xu et al., 2009 |
|       |                   | hrcA | Conserved ATP-dependent proteases of C. jejuni to stress tolerance and virulence | Chon et al., 2007 |
|       |                   | racRS | Salinity stress tolerance - ascorbate-glutathione peroxidase | Kang et al., 2013 |
|       |                   | ctpB | Protease ATP-dependent (E. coli CtpA) • ATPase activity | Parsell and Lindquist, 1993 |
|       |                   | ppk1 | The adenylate cyclase gene MaAC/membrane location of the protein | Sarasbhi et al., 2015; Gangsai et al., 2010 |
|       |                   | ppk2 | Arabidopsis genes | Auesukaree et al., 2009 |
| 3     | Nutrition Depletion/Starvation | htrB | ATP binding cassette transporter components PaqP and PaqQ in bacterial salt stress tolerance | Lin et al., 2009a |
|       |                   | ppk1 | Inhibiting polyphosphate kinase | Sarasbhi et al., 2015; Svensson et al., 2008; Svensson et al., 2009 |
| 4     | Osmotic Tolerance | htrB | ATP binding cassette transporter components PaqP and PaqQ in bacterial salt stress tolerance | Lin et al., 2009b |
| 5     | Low pH/Acid Tolerance | htrB | ATP binding cassette transporter components PaqP and PaqQ in bacterial salt stress tolerance | Sarasbhi et al., 2015 |
| 6     | Oxidative Stress/Oxygen Stress | spoT | Quorum sensing genes/inhibiting polyphosphate kinase | Parsell and Lindquist, 1993 |
|       |                   | hspS | Proteomics Analysis of Drought Stress-Responsive Proteins | Parsell and Lindquist, 1993 |
|       |                   | htrA | stress-responsive cyclophilin gene | Chen et al., 2007 |
|       |                   | fdaA | Resistance to peroxynitrite and stage-specific survival in macrophages | Master et al., 2002 |
|       |                   | sodB | Additionally influences biofilm formation | Svensson et al., 2009 |
|       |                   | dcuA | | |
|       |                   | dps | | |
|       |                   | katA | | |
|       |                   | perR | | |
|       |                   | ahpC | | |
|       |                   | sodB-ahd | | |
|       |                   | cj1556 | | |
|       |                   | cj1546 | | |
|       |                   | cj1556-cj1386 | | |
most highly conserved protein-coding genes known to be involved (Tang et al., 2017). Chaperone proteins may be involved in aerobic + acid denaturation or damage repair of proteins. Chaperone based GroEL and DnaK heat shock protein (HSPs) have been described as caused under acid conditions in *Salmonella typhimurium* (Ghazaei, 2017), which plays a major role after mild stress, either in the prevention of subsequent DNA damage or in the repair of already damaged DNA. The reported protein response were found to be closely associated with following pathogens such as *S. typhimurium* (Ghazaei, 2017), *Escherichia coli* (Burt et al., 2007) and *Acinetobacter baumannii* (Cardoso et al., 2010). This global reaction, in *C. jejuni*, which induced various mechanisms of survival and offers an initial insight into mechanisms that contribute to resistance of aerobic + acid susceptibility.

ATR-related RpoS: Transcription controller σs, encoded by the rpoS gene (RNA polymerase sigma factor), is a replacement sigma factor, the amount of which increases dramatically during any permanent stage of the microbes. The increase in σs concentration and gene expression is known to influence acid-shock proteins, such as high osmolality, low pH, hydration, and oxidation in cell survival (Ferreira et al., 2001). Sudden increases in cell acidification also cause strong increases in rpoS levels. Mutants that are defective in rpoS or that generate low concentrations of rpoS are highly susceptible to acidic conditions.

**Salt-Tolerance Mechanisms**

Sodium chloride (NaCl) is one of the most used preservatives in the food industry. *C. jejuni* is highly responsive to high osmolality compared to most other enteric microbes (Feng et al., 2018; Kovacs et al., 2019). *C. jejuni* is unable to multiply with ≥2% NaCl at 42°C, but can multiply in the presence of 0.5% to 1.5% NaCl at 42°C (Gomes et al., 2018). Lake et al. (2019) reported that *C. jejuni* could tolerate 7.5% sodium chloride (NaCl) in media at 4°C better than at 22–30°C as measured using bioluminescence. In microarray analysis, Zhao et al. (2019) found that *C. jejuni* had augmented expression of oxidative-stress genes and heat-shock genes after exposure to hyperosmotic conditions.

**Genetic Regulation by Sigma Factors**

*C. jejuni* has a genome size of 1.4 Kbp, coding for approximately 1731 genes. In contrast to other environmental and food pathogens that have several gene-regulation processes occurring via sigma factors, *C. jejuni* has only three sigma factors (Wöst et al., 1998; Parkhill et al., 2000; Carrillo et al., 2004), and no recorded extracytoplasmic-function (ECF) sigma factors. The three sigma variables account for most operations related to gene regulation. Sigma 70 or RpoD is the housekeeping sigma factor that regulates most *C. jejuni* promoters. The other two sigma factors, sigma 28 (FilA, Filament A) and sigma 54 (RpoN), regulate 44 different genes that are mostly related to flagellar synthesis and protein secretion (Studholme and Dixon, 2003; Porcelli et al., 2013). The regulatory mechanisms and nucleic-base composition of the sigma-factor promoters were detailed by Petersen et al. (2003). Major promoters recognized by *C. jejuni* sigma subunits have the –10 element, whereas there is no consensus for the –35 element. The regulatory roles of RpoN in *C. jejuni* under various stress conditions were shown using RpoN mutation and complementation in a study by Hwang et al. (2011). FilA is thought to regulate motility as well as the virulence of *C. jejuni* (Carrillo et al., 2004). Thorough genomic research into these mutant strains is required to elucidate the intricacies of gene regulation among the three sigma variables in this uncommon pathogen. Furthermore, how the lack of conservation of the –35 element contributes to optimal transcription in vivo remains to be determined. Morphological differences may exist, such as the conversion of a spiral bacterium to a coccus-/rod-shaped bacterium under osmotic and cold stress (Carrillo et al., 2004; Hwang et al., 2011). Even if *C. jejuni* is regarded as a pathogen transmitted *via* meat and poultry, it is not very tolerant to several nonoptimal conditions, particularly desiccation and osmotic stress.

**Role of Osmolytes in Cryotolerance**

Compared with *Salmonella* spp. and *E. coli*-like enteric bacteria, little is known about the mechanisms that enable survival of *Campylobacter* spp. under various environmental and stress conditions. A previous study found that *C. jejuni*’s ability to influence gene expression after exposure to environmental stress was a barrier to comparison with other bacteria (Park, 2002). Rapid temperature decreases cause bacteria to express a distinct set of proteins, and this response is known as cold shock. These proteins are predominantly nucleases, helicases, and ribosome-related elements that communicate with and bind to RNA and DNA. Cold-shock proteins induce a membrane adaptation, cold signal sensing, and translation-device alteration (Ultee et al., 2019). Ultee et al. (2019) reported motility for oxygen consumption, protein synthesis, and *C. jejuni* survival capacity at 4°C. Lu et al. (2011) revealed that *C. jejuni* survive at in low-temperature. This indicates that *C. jejuni* may produce a cold-shock effect that influences low-temperature gene expression to 4°C. CspA is the main cold-shock protein in *C. jejuni*, and functions as an RNA chaperone to enhance more effective cold-shock protein translation (Parkhill et al., 2000; Giuliodori et al., 2010). It is not yet clear how *C. jejuni* respond to or regulate the expression of genes during cold shocks. Based on documented studies, the cold-shock reaction is presented as a complex system of genes that are regulated by the same stimulus, where post-transcriptional conditions are essential. *C. jejuni* poses problems to food security and public health in the food-processing industry, since it survives for several months at 4°C. *C. jejuni* declined by about 1 log cfu/ml when stored at 4°C for seven days (Guèvremont et al., 2015; Lake et al., 2019). Oxidative stress can upregulate cold-shock protein expression, which can extend the life span of *C. jejuni* in hypothermal conditions (Karki et al., 2019).

**Survival During Ultraviolet (UV) Stress**

VBNC refers to a state in which conventional culture on enhanced agar media does not detect microbial cells, although it remains feasible to resuscitate the microbes under preferential circumstances. This unique survival strategy has been shown to exist in nature (Salma et al., 2013). More than 60 different bacterial species have been found to be VBNC, including both Gram-negative (e.g., *E. coli*, *S. enterica*, *C. jejuni*, *H. pylori*, *Pseudomonas*...
luteus could help improve the microbiological quality of raw chicken. Overall, UV application of packaging and surface materials. These data indicated reduction in Campylobacter isolates following UV treatment. In UV-treated (0.192 J/cm) fresh chicken fillet, C. jejuni was decreased by 0.76 cfu/g, whereas, a reduction in C. jejuni of up to 3.97 log cfu/cm was attained with UV treatment of packaging and surface materials. This data indicated that Campylobacter is UV-prone, but concerning differentials occurred among the studied isolates. Overall, UV application could help improve the microbiological quality of raw chicken and remove contamination of related surfaces and packaging (Haughton et al., 2011).

Investigations were conducted concerning organism survival in rivers, coastal waters, and sewage to investigate the natural and artificial habitats of C. jejuni with UV-B light (280–315 nm) (Hénault-Ethier et al., 2016; García-Peña et al., 2017; Otigba et al., 2018). Another research project in conjunction with these revealed that C. jejuni was susceptible to UV-C light (254 nm). UV sensitivity was greater than that of other microbes (Butler et al., 1987). The application of UV-C radiation to decrease C. jejuni in chicken breast also attracted interest (Rodrigues et al., 2019), as well as in broiler meat (Zhuang et al., 2019) and ready-to-eat ham (Yang et al., 2017). UV-light techniques have been extensively explored for reducing micro-organisms, including Campylobacter, in foodstuffs (Rodrigues et al., 2019; Zhuang et al., 2019).

UV irradiation achieved a maximal reduction of C. jejuni on broiler meat and broiler skin of 0.7 and 0.8 log, respectively. The maximal decrease by UV irradiation on broiler carcasses (254 nm, 32.9 m W/s per square inch) was 0.4 log, and the combination of UV and activated oxygen also achieved a 0.4 log reduction in C. jejuni. The primary sanitation method for C. jejuni in broiler carcasses cannot rely on UV irradiation alone or in conjunction with activated oxygen. However, application of these methods in conjunction with other sanitation techniques, as well as the adequate processing and sanitation of processing plants, may be more efficient than the use of these processes to reduce C. jejuni on broiler carcass surfaces (Isihannou and Lyhs, 2009). UV irradiation was less efficient at removing C. jejuni on broiler meat and skin than on agar plates. It reduces C. jejuni on grilled skin a little more effectively than on meat. Dry meat undergo ultraviolet radiation has low invasive capacity, and the cutting edges of food perhaps produced shade that interfered with UV irradiation (Rodrigues et al., 2019). The fibers could be isolated by swabbing the surfaces and allowing the swabs to absorb humidity from below the meat layer. After flaming, the skin did not appear to have changed much, and bacteria could not have crossed the threshold skin into the meat. Wong et al. (1998) also indicated that gram positive bacteria were more efficiently reduced by UV irradiation. However, the effects of UV irradiation can differ considerably in C. jejuni isolates from different origins and at different growth stages (Yaun et al., 2003).

Oxidative Stress and Aerotolerance
Campylobacter does not usually grow in environments of atmospheric oxygen (air) due to it being microaerophilic and requiring 5–10% carbon dioxide (CO2) (Fridrich et al., 2019). Campylobacter can tolerate oxidative stress even after exposure towards aerobic conditions (Kim et al., 2015). Microaerophilic environment generates favorable growth conditions for C. jejuni (Geng et al., 2019). Karki et al. (2019) found that subcultures of C. jejuni could develop colonies on blood agar at 4, 37, and 42°C in air conditions. This exposure to aerobic conditions leads to the transformation of both the cell morphology and the pattern of the external membrane proteins. Their results indicated that the bacterial cells had high survivability in aerobic conditions compared to microaerobic conditions. Geng et al. (2019) reported that subcultures of C. jejuni from both sterile chicken mince and stream water developed colonies at 5, 25, and 37°C on blood agar, and that cells were more likely to survive when cultured in a microaerophilic than an aerobic environment.

In comparison with microaerobic conditions owing to oxidative pressure, C. jejuni showed external structural changes in the form of coccoid morphology (Oh et al., 2015), and the inner ATP synthesis of C. jejuni decreased with oxidative stress (Cain et al., 2019). Under microaerophilic environments, C. jejuni may develop better than under oxygenic conditions at a cell concentration of <10⁵ cfu/ml (Kaakoush et al., 2007).

C. jejuni Heat-Shock Response
Heating is one of the sanitizing techniques used for food preservation in the food sector. Heat treatment readily reduces the survival of C. jejuni relative to other enteric micro-organisms. For C. coli, decimal reduction times (D-values) were 381, 89, 21.9, and 5.7 s at 49.9, 55.4, 60.0, and 62.5°C, respectively, in phosphate buffer saline (PBS) (Habib et al., 2010; Upadhyay et al., 2019). Treatment of C. jejuni at 55°C for 3 min, decreased the density by 2–3 log cfu/ml (Kovacs et al., 2019). Heat treatment caused C. jejuni to lose its invasion capacity, and upregulate transcriptional factor HrcA for acid shock (Xu et al., 2019).

Desiccation Tolerance
Tolerance to desiccation in Campylobacter spp. was first reported by Fernandez et al. (1985) in several biotypes of C. coli and C. jejuni subjected to 2–8 hours of exposure. The RpoN sigma factor does not significantly contribute to the tolerance to osmotic shock or desiccation, whereas tolerance of cold or refrigeration temperatures can be directly correlated with bacterial survival capacity in cold environments (Burgess et al., 2016). The extreme sensitivity to desiccation and poor tolerance to heat and drying established that blowing hot air was an efficient method to prevent carrying dormant C. jejuni from poultry to human hosts in commercial settings (Berrang et al., 2011). Such methods could be applied to farms to prevent pathogenic carriers through poultry.

Biofilm Formation and Stress Adaptation
Extracellular polysaccharide (EPS) accumulation leads to biofilm formation by microbes, biofilm formation could allow additional species to accumulate on surfaces (Simoes and Simões, 2013;
EPSs compressed of nucleic acids, polysaccharides, proteins, phospholipids, and teichoic acids to form biofilms (Miao et al., 2019). Many factors stimulate biofilm formation, including temperature, NaCl, pH, compounds of food, and type of surface (Arnold and Silvers, 2000; Nguyen et al., 2006; Speranza et al., 2011; Vázquez-Sánchez et al., 2013; Mavri et al., 2016; Whitehouse et al., 2018; Longo and Spano, 2019; Xu et al., 2019). Biofilms can form on dairy-product-handling machinery and nutrition-handling surfaces (Miao et al., 2019), and can therefore contribute to the occurrence of foodborne diseases and create a public health issue (Maes et al., 2019; Miao et al., 2019). There are numerous reports on foodborne diseases in relation to biofilm development (Metselaar et al., 2015; Mavri et al., 2016; Whitehouse et al., 2018; Ma et al., 2019). Microbes in biofilms are more resistant to antibiotics than plankton cells are (Stewart and Costerton, 2001; Olsen, 2015).

C. jejuni preconditions define their environment for growth, and Surface attachment and biofilm generation are vital tools for environmental stability (Dykes et al., 2003), as shown in Figure 4.

C. jejuni can generate biofilms in liquid media as a monospecies (Salama et al., 2018) in aerobic conditions (Ovesen et al., 2019) C. jejuni can form biofilms both as a monospecies and as a combination of microbes (The et al., 2019) and nutritional components (Bronnec et al., 2016). Salama et al. (2018) showed that the aggregating and pellicle form of C. jejuni that forms at 30–37°C in a microaerobic environment allows the bacteria to survive under aerobic conditions. Ovesen et al. (2019) demonstrated that C. jejuni easily creates biofilms, and that flagellar motility aggravates biofilm production. It currently reads as though it is the report of Ovesen et al., 2019 stated that C. jejuni could acclimate to develop a biofilm linked to CsrA under aerobic conditions (Askoura et al., 2016; Ye et al., 2019). Therefore, CsrA mutation leads to inhibition of biofilm formation (Fields and Thompson, 2008). C. jejuni can also contribute to biofilm formation in combination with other microbes under a microaerobic environment, but the combination is specific to the microbes and the environment (The et al., 2019), for example the poultry environment is an example of this specific environment/microbe combination. The biofilm formation capacity of C. jejuni depends on culture media, oxidative stress, temperature, and interspecies composition (Bronnec et al., 2016). Protein generation, quorum sensing, and flagellar sensing also influence the capacity of C. jejuni to generate biofilms, as shown in Table 1.

**Antibiotic Susceptibility of C. jejuni**

Antibiotics are typically used to fight against bacterial infections (Pedersen et al., 2018), and possess different mechanisms to kill or inhibit bacteria. For example, quinolones, such as nalidixic acid, dysregulate DNA synthesis in microbial cells (Jacoby, 2005), whereas macrolides, including erythromycin, bind to ribosomes in the microbes, blocking elongation of the peptide loop (Arsic et al., 2018). Severe cases of campylobacteriosis require adequate treatment with antibiotics (Wieczorek and Osek, 2013), usually a fluoroquinolone and macrolide combination (Devit et al., 2019). Improper and frequent antibiotic use has led to increased antibiotic resistance in Campylobacter, which is a public health issue. Consequently, the fluoroquinolone and macrolide efficacy can fail to overcome the antibiotic resistance of Campylobacter (Pedersen et al., 2018; Bolinger et al., 2018; Silvan et al., 2018; Devit et al., 2019). The continuous usage of antibiotics such as tetracycline, ciprofloxacin, and erythromycin leads to the development of resistance in enteropathogens; specific resistance genes to these antibiotics were identified in C. jejuni isolates (Wirz et al., 2010), and comparable trends in C. coli were reported in Canada (Devit et al., 2019). Zwe et al. (2018) found

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**FIGURE 4** | Process of biofilm formation.
that \textit{C. jejuni} isolated from ducks in Singapore was resistant to ciprofloxacin (86.7%), nalidixic acid (84.4%), and erythromycin (11.1%) (Devi et al., 2019). The development of antibiotic resistance in \textit{Campylobacter} means the treatment regime of campylobacteriosis will involve other antibiotics, like gentamycin (Aarestrup and Engberg, 2001; Pedersen et al., 2018).

**CONCLUSION**

\textit{Campylobacter} use a range of approaches for environmental and genomic survival, and molecular studies have facilitated a better understanding of these processes. Genetic modifications within the species \textit{C. jejuni} have been significantly targeted, and genome sequencing for this species has been completed. Epidemiological studies and phenotypical analyses found variations in the incidence of strains of \textit{C. jejuni}, or environmental circumstances between strains of \textit{C. jejuni}. It has been easier to understand mechanisms that affect \textit{C. jejuni} persistence by examining the transformation of this important pathogen in natural settings, such as soil and water, and combining connections with environmental changes. However, the reported differences in various strains of \textit{C. jejuni} highlight the constraints of drawing generalized conclusions from individual strain research.

The multiple stress responses of \textit{Campylobacter} spp. may facilitate survival in extreme environmental conditions, in addition to increasing resistance to subsequent traumatic conditions, which might enhance acquisition of virulence genes. Our review demonstrates the contribution of stress-tolerance responses to the resistance and pathogenicity of \textit{C. jejuni}. Minor factors involved in stress management based on stress-responsible protein production are also involved in the activation and up- or down-regulation of virulence genes, and may contribute to the pathogenesis of \textit{C. jejuni}. This finding is based on reported studies validated in different isolates of \textit{C. jejuni} in response to stress adaptation, therefore caution should be taken in segregating and characterizing strains of \textit{C. jejuni}. Gram-negative microaerophilic bacteria like \textit{H. pylori} and \textit{C. jejuni} are extremely common, and are human gastrointestinal pathogens. Only by combining these separate strands can the role of environmental survival in transmitting these important pathogens be fully understood.

**Required Future Research to Fill Current Knowledge Gaps**

Major gaps in current research on stress responses on \textit{C. jejuni}, so far, researchers have predominantly focused on antibiotic resistance and oxidative stress in \textit{C. jejuni}. However, various other stress conditions and specific survival-mechanism-based evolutionary adaptation methods exist to overcome modern preservative conditions, such as acidity, alkalinity, osmotic imbalance, freezing, high temperatures, UV light, and dryness (reduced water content). Future research should concentrate on understanding the genetic make-up of \textit{C. jejuni} that helps this organism survive various environmental conditions. Identification of these evolutionary adaptive mechanisms and specific signaling pathways will assist future researchers in developing effective methods to overcome the adaptive mechanism(s) of \textit{C. jejuni}. Furthermore, understanding \textit{C. jejuni} stress-oriented genes and their specific expression mechanisms based on environmental stressors have implications in biofilm interactions and their signaling mechanism(s), and in practical terms this could help with current technological hurdles in the food system.

**AUTHOR CONTRIBUTIONS**

The manuscript was written in detail and sectioned for specialized discussion with the respective authors in the field of research. Designing the outline of the review manuscript (Multiple stress tolerance in \textit{Campylobacter jejuni}), visualization, and conceptualization—S-HK, RC, D-HO. Cross-protection and other general survival mechanisms towards environmental stress—SR.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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