Non-selective regulation of peroxide and superoxide resistance genes by PerR in *Campylobacter jejuni*

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**INTRODUCTION**

*Campylobacter jejuni* is one of the leading bacterial causes of gastroenteritis worldwide (Young et al., 2007). *C. jejuni* infection also accounts for the majority (approximately one quarter) of disease cases of Guillain-Barré syndrome, an acute peripheral neuropathy, as a post-infection complication (Hughes and Cornblath, 2005). *C. jejuni* is a commensal bacterium in the intestines of poultry that do not develop any clinical symptoms (Moore et al., 2005); thus, human infections with *C. jejuni* are frequently caused by the consumption of contaminated poultry (Allos, 2001). *C. jejuni* requires low oxygen concentrations (3 – 13%) for growth and is sensitive to high oxygen tension under normal atmospheric conditions. *C. jejuni* favorably inhabits the gastrointestinal tracts in poultry that provide optimal growth temperatures (about 42°C), nutrients, and low oxygen levels. Once excreted from animals, however, *C. jejuni* encounters various harsh environmental stress, such as high oxygen tension and nutrient starvation. Particularly, increased oxidative stress in the atmosphere is a critical barrier that *C. jejuni* should overcome during its zoonotic transmission from animals (i.e., poultry) to humans via food. Therefore, a better understanding of the molecular mechanisms of oxidative stress is critical for elucidating the infection process of this microaerophilic foodborne pathogen.

*C. jejuni* has a unique oxidative stress defense system. For the detoxification of reactive oxygen species (ROS), for example, *C. jejuni* possesses only single copies of alkyl hydroperoxide reductase (*ahpC*), catalase (*katA*), and superoxide dismutase (*sodB*) (Atack and Kelly, 2009), whereas other bacteria often harbor redundant types of these antioxidant genes. *Escherichia coli* encodes three *sod* genes (*sodA, sodB*, and *sodC*) and two catalase genes (*katE* and *katG*) (Imlay, 2008). Alkyl hydroperoxide reductase in *E. coli* consists of two subunits, AhpC and AhpF (Poole et al., 2000), whereas *ahpF* homologs are absent from the *C. jejuni* genome (Baillon et al., 1999). *C. jejuni* also has unique regulatory mechanisms for oxidative stress resistance. In *E. coli* and *Salmonella*, OxyR and SoxRS regulate expression of peroxide and superoxide defense regulons, respectively (Imlay, 2008; Chiang and Schellhorn, 2012). However, *C. jejuni* lacks homologs of SoxRS and OxyR (Atack and Kelly, 2009). Instead, *C. jejuni* possesses PerR, a substitute for OxyR found in many Gram-positive bacteria and some Gram-negative bacteria; in fact, *C. jejuni* is the first Gram-negative bacterium that is known to harbor PerR (Van Vliet et al., 1999). In *C. jejuni*, PerR inactivation significantly increases the expression of peroxide resistance enzymes, such as AhpC and KatA, and renders *C. jejuni* hyper-resistant to H$_2$O$_2$ (Van Vliet et al., 1999).
PerR belongs to the ferric uptake regulator class of metal-responsive repressor proteins (Van Vliet et al., 1999; Lee and Helmann, 2007). PerR uses either manganese or iron as a regulatory metal cofactor to detect oxidative stress in *Bacillus subtilis* (Lee and Helmann, 2006; Iacquamet et al., 2009), whereas iron, but not manganese, affects *perR* transcription by PerR autoregulation in *C. jejuni* (Kim et al., 2011). Although PerR is the key regulator of oxidative stress defense in *C. jejuni*, the regulatory mechanism of PerR has not been fully defined in this microaerophilic foodborne pathogen, particularly under oxidative stress (e.g., aerobic conditions). In this study, we demonstrated that PerR controls the transcription of *sodB*, the most important gene in superoxide resistance, and plays a critical role in non-selective regulation of peroxide and superoxide resistance genes in *C. jejuni*.

**MATERIALS AND METHODS**

**BACTERIAL STRAINS AND GROWTH CONDITIONS**

*C. jejuni* NCTC 11168 and its derivatives were grown at 42°C on Mueller-Hinton media (Difco) under microaerobic conditions (5% O2, 10% CO2, 85% N2). Kanamycin (50 μg/ml) was occasionally added to the culture media where required. Broth cultures were grown by shaking at 200 rpm aerobically or microaerobically.

**QUANTITATION OF INTRACELLULAR ATP LEVELS**

The intracellular ATP levels were measured by using the ATP Bioluminescent Assay Kit (Sigma) according to the manufacturer’s instructions. Briefly, after washing with PBS (pH 7.4) twice, the *C. jejuni* suspension was mixed with the same volume of the ATP assay solution in a 96-well plate. After incubation at room temperature for 3 min, the luminescence was measured with FLUOstar Omega (BMG Labtech). The total protein concentrations of the sample were measured by using the Bradford assay (Bradford, 1976) to normalize the ATP levels to the protein amounts. The experiments were repeated three times, and each set was run in triplicate.

**FLUORESCENCE MICROSCOPIC ANALYSIS**

*C. jejuni* was harvested after 4 h, 8 h, and 24 h culture under aerobic or microaerobic conditions and was stained with the LIVE/DEAD BacLight™ bacteria viability kit (Life Technologies). Images were visualized with a fluorescence microscope (Carl Zeiss M1) and were analyzed with Axio Vision LE (Zeiss).

**CONSTRUCTION OF lacZ TRANSCRIPTIONAL FUSION AND β-GALACTOSIDASE ASSAY**

The promoters and partial coding regions of *ahpC*, *katA*, and *sodB* were PCR-amplified with the primer pairs of *ahpC_PF_F*(XbaI) and *ahpC_PF_R*(XbaI), *katA_PF_F*(XbaI) and *katA_PF_R*(XbaI), and *sodB_PF_F*(XbaI) and *sodB_PF_R*(XbaI), respectively (Table 1). The PCR products were cloned into an XbaI site of pMW10 (Wösten et al., 1998) that contains a promoterless lacZ gene. Each fusion plasmid was mobilized to *C. jejuni* NCTC 11168 by conjugation. *C. jejuni* strains harboring a P*perR*-lacZ plasmid and a perR complementation strain were described in our previous study (Kim et al., 2011). Occasionally, the assays were performed with Minimum Essential Medium alpha (MEMα) (Life Technologies), which does not contain iron, in the presence or absence of 40 μM FeSO4 (Sigma). To assess the effect of oxidative stress on the promoter activities of *ahpC*, *katA*, and *sodB*, β-galactosidase assays were carried out with oxidants, such as H2O2, cumene hydroperoxide (CHP, an organic peroxide), and menadione (MND, a superoxide generator). Briefly, *C. jejuni* in the exponential phase was harvested and resuspended in fresh MH broth to a cell concentration of 10⁹ CFU/ml, and was exposed to oxidants for 2 h prior to the assay.

| Primer        | DNA sequence from 5’ to 3’ |
|---------------|---------------------------|
| ahpC_PF_F     | TCTCCACCTCCTGTAGTTGTTAGCATC |
| ahpC_PF_R     | CGCTGGAGCTTGAAGATCTGAGGGC |
| sodB_PF_F     | AGTATGCTAGCTCAGAACAACCTTTTTC |
| sodB_PF_R     | TCCCATGATATCTAGAAGTTCTCC |
| katA_PF_F     | TAAAACAGCTCTAGAAGGATGATTTTC |
| katA_PF_R     | TTGAATTTTGGGTATCATCTAGAAGTTCTCC |
| SB_P          | GCGAAGGATCTCAGAATGCTGATGATA |
| SB_R          | AGATAACGAAATGCTTTTGTAT |

**PURIFICATION OF RECOMBINANT PerR PROTEIN (rPerR)**

Purification of rPerR was performed as described in our previous study (Kim et al., 2011). Briefly, an *E. coli* strain carrying pET15b::perR was grown in Luria-Bertani (LB) broth to an optical density at 600 nm of 1.0 at 37°C, and 1 mM IPTG (isopropyl-β-D-thiogalactopyranoside) was then added. After 5 h induction at 37°C, cells were harvested and resuspended in lysis buffer (20 mM Tris-HCl [pH 8.0], 300 mM NaCl). Bacterial cells were lysed by sonication and purified under native conditions using Ni²⁺ affinity chromatography (Qiagen). The His-tag was removed from rPerR with the Thrombin Cleavage Capture Kit (Novagen) according to the manufacturer’s instructions.

**ELECTROPHORETIC MOBILITY SHIFT ASSAY (EMSA)**

EMSA was performed as described previously with some modifications (Iacon and Zhang, 2007). The Cy3-labeled DNA probes were PCR-generated with the primers of SB-P and SB-R (Table 1). The DNA probe was incubated with rPerR at different concentrations at 37°C for 15 min in 10 μl of gel-shift assay buffer (20 mM HEPES [pH 7.6], 1 mM EDTA, 10 mM (NH4)2SO4, 5 mM DTT, 0.2% Tween 20, 30 mM KCl, 0.1 μg poly dl-dC). The reaction mixtures were resolved in a 6% polyacrylamide gel, and the Cy3-labeled DNA fragments were visualized with FluorChem™-R (ProteinSimple, USA).

**RESULTS**

**DIFFERENTIAL INDUCTION OF ahpC, katA, AND sodB TRANSCRIPTION UNDER AEROBIC CONDITIONS**

AhpC, SodB, and KatA are the sole alkyl hydroperoxide reductase, superoxide dismutase (SOD), and catalase in *C. jejuni*, respectively, significantly contributing to oxidative stress defense in *C. jejuni* (Atack and Kelly, 2009). Although *C. jejuni* is a
microaerophilic bacterium, it harbors a certain level of aero-tolerance (Gundogdu et al., 2011). Due to the importance of ahpC, katA, and sodB in ROS detoxification, we hypothesized that C. jejuni would differentially regulate ahpC, katA, and sodB expression to scavenge toxic ROS under aerobic conditions. To measure the transcriptional levels of ahpC, katA, and sodB, we constructed transcriptional fusions of the ahpC, katA, and sodB promoters to a promoterless lacZ in pMW10 (Wösten et al., 1998). Although C. jejuni growth was significantly decreased under aerobic conditions (Figure 1A), interestingly, the transcriptional levels of ahpC and sodB were increased under aerobic conditions (Figure 1B). After 24 h culture under aerobic conditions, the promoter activities of ahpC and sodB were increased by approximately 62% and 89%, respectively, compared to microaerobic conditions (Figure 1B).

Despite a significant growth defect under aerobic conditions, C. jejuni exhibited a substantial increase in the transcriptional levels of the antioxidant genes. The intracellular ATP levels were measured to examine the physiological activity of C. jejuni under aerobic conditions. The ATP concentrations were approximately 16-fold higher under microaerobic conditions than aerobic cultures after 24 h (Figure 1C), indicating that C. jejuni is not physiologically active under aerobic conditions. Microscopic observation with the LIVE/DEAD staining revealed that most viable C. jejuni cells were in coccoid forms under aerobic conditions (Figure 1D). Based on the morphology and ATP levels, C. jejuni is likely to enter a viable-but-non-culturable (VBNC) state under aerobic conditions.

**ABROGATION OF OXIDANT-MEDIATED INDUCTION OF ahpC, katA, AND sodB BY A perR MUTATION**

Since the transcriptional levels of ahpC, katA, and sodB were increased under aerobic conditions (Figure 1C) and the common biological role of the antioxidant genes is ROS detoxification, we hypothesized the augmented transcriptional levels in ahpC, katA, and sodB under aerobic conditions would result from increased oxidative stress in C. jejuni. Thus, we investigated whether oxidants would increase the promoter activity of the ROS-detoxification genes. The promoter activities of ahpC, katA, and sodB were monitored in the presence of oxidizing agents, such as H2O2, CHP (an organic peroxide), and MND (a superoxide anion generator). Regardless of the oxidant type, whether peroxide or superoxide, the transcription of ahpC, katA, and sodB was induced by oxidant exposure (Figure 2). The transcriptional induction by oxidants occurred in a concentration-dependent manner, and antioxidant treatment removed the oxidant-mediated induction of ahpC, katA, and sodB transcription (Supplementary Figure 1).

Since PerR is a major regulator of oxidative stress in C. jejuni (Van Vliet et al., 1999), we investigated if PerR could be associated with the transcriptional changes in the mutants under oxidative stress. Interestingly, the transcriptional induction of ahpC, katA, and sodB by oxidants completely disappeared in the perR mutant (Figure 2), indicating that PerR is associated with the transcriptional changes in ahpC, katA, and sodB under oxidative stress. In addition, the perR mutation increased the transcriptional levels of ahpC, katA, and sodB (Figure 2), suggesting that the perR mutation de-repressed the antioxidant genes, even including sodB. These results strongly suggest that PerR plays a role in the transcriptional control of both peroxide- and superoxide-d detoxification genes in C. jejuni under oxidative stress conditions.

**PerR REGULATION OF sodB TRANSCRIPTION**

Since a perR mutation affected sodB transcription (Figure 2B), we further investigated if PerR regulates sodB transcription by performing the PsodB-lacZ promoter fusion assay. A perR mutation de-repressed sodB transcription, regardless of the presence or absence of iron, and perR complementation restored sodB transcription to the wild-type level (Figure 3A). The increase in sodB transcription by the perR mutation was more significant in ME49 than in MH broth (data not shown). To examine if PerR regulates sodB by binding to the sodB promoter, a gel-shift assay was performed with rPerR. Interestingly, rPerR directly bound to the sodB promoter (Figure 3B). A putative PerR binding site was predicted in the sodB promoter region based on the conserved PerR binding site in C. jejuni (Kim et al., 2011; Figure 3C). Taken together, these data suggest that PerR regulates sodB transcription by binding to the sodB promoter.

**ALTERATION OF perR TRANSCRIPTION BY OXIDANTS AND AERATION**

Since the perR mutation completely removed the oxidant-mediated induction of ahpC, sodB, and katA (Figure 2), we investigated if perR transcription is affected by oxidants. The PsperR-lacZ fusion assay was conducted with ME49, because iron reduces perR transcription in C. jejuni (Kim et al., 2011). Oxidative stress, including oxidants (i.e., H2O2, organic peroxide, and superoxide) and aeration, substantially decreased the levels of perR transcription (Figure 4). The reduction of perR transcription by oxidative stress was not influenced by iron, although iron decreased the levels of perR transcription (Figure 4). The reduction of perR transcription by aeration would result from the increased ROS accumulation under aerobic conditions. The results clearly showed that perR transcription is affected by oxidative stress in C. jejuni.

**DISCUSSION**

PerR is a primary regulator of peroxide stress defense in many bacteria. In order for PerR to control the expression of peroxide stress defense genes, bacteria should control the intracellular level of PerR in response to peroxide stress. However, previous observations in other bacteria have shown that perR transcription is not affected by H2O2. For example, a transcriptomic analysis in Staphylococcus aureus demonstrated that the transcription of perR and its regulatory genes is not altered by H2O2 exposure (Chang et al., 2006). In B. subtilis, perR transcription is not changed by H2O2 (Fuangthong et al., 2002); instead, PerR regulates peroxide resistance genes by protein conformational changes under peroxide stress (Herbig and Helmann, 2001). B. subtilis PerR senses H2O2 by oxidation of one of two histidine residues (i.e., H37 and H91) that coordinate the bound Fe2+; this modification results in the dissociation of Fe2+ from PerR. The demetallated PerR cannot bind to DNA, and this conformational changes in PerR induces gene expression (Lee and Helmann, 2006). Interestingly, in this study, we demonstrated that oxidative stress, such as oxidant exposure and aerobiosis, directly reduced the levels of perR.
transcription (Figure 4). To the extent of our knowledge, C. jejuni perR is the only perR homolog whose transcription is known to be affected by oxidative stress. Although PerR is considered as a peroxide resistance regulator, perR transcription was altered by exposure to both peroxides (H2O2 and CHP) and superoxide (MND; Figure 4). Since PerR represses ahpC and katA (Van Vliet et al., 1999) and sodB (Figure 3), down-regulation of perR transcription under oxidative stress will de-repress ahpC,
**katA** and **sodB**. Consistently, we observed that the transcriptional levels of **ahpC**, **katA**, and **sodB** were increased by aeration and oxidant exposure (Figures 1, 2), and a **perR** mutation abrogated the transcriptional response of **ahpC**, **katA**, and **sodB** to oxidants (Figure 2), suggesting that PerR is a key player in the induction of both peroxide- and superoxide-detoxification genes under oxidative stress.

In this study, we demonstrated that PerR negatively regulates **sodB** expression (Figure 3). Based on the promoter sequence of **sodB** in **C. jejuni** (Pesci et al., 1994), a predicted PerR-binding site overlaps with the -10 region of the **sodB** promoter (data not shown); thus, PerR binding would interfere with **sodB** transcription. PerR is known as a regulator of peroxide resistance. However, our findings revealed that PerR also regulates **sodB** transcription in **C. jejuni**. To the best of our knowledge, this report is first describing direct regulation of **sodB** transcription by PerR. As a key enzyme of superoxide resistance, SOD catalyzes the dismutation of superoxide to H$_2$O$_2$. Due to its physiological importance in oxidative stress defense, bacteria often harbor redundant types of SOD. For example, **E. coli** contains three types of SOD, including two cytoplasmic SOD isoenzymes [**SodA** (Mn-cofactored SOD) and **SodB** (Fe-cofactored SOD)] and a periplasmic SOD [**SodC** (Cu/Zn-cofactored SOD)] (Imlay, 2008). However, SodB is the sole SOD present in **Campylobacter** (Pesci et al., 1994; Purdy and Park, 1994), significantly contributing to **Campylobacter**’s stress resistance and colonization of chicken intestines (Pesci et al., 1994; Palyada et al., 2009). Various mechanisms for the regulation of sod genes have been reported in different bacteria. In **E. coli** and **S. enterica**, exposure to superoxide-generating agents increases SodA expression through positive regulation by SoxRS (Greenberg et al., 1990; Pomposiello et al., 2001); however, **C. jejuni** lacks the SoxRS system (Parkhill et al., 2000); in this study, we demonstrated another novel mechanism of **sodB** regulation by PerR in **C. jejuni**.

Since **C. jejuni** is a microaerophilic bacterium, prolonged exposure to aerobic conditions substantially reduced the growth of **C. jejuni**; aerobic growth for 24 h resulted in an approximate 5-log reduction in colony forming units (Figure 1A). However, the transcriptional levels of **ahpC**, **katA**, and **sodB** were higher under aerobic conditions than microaerobic conditions (Figure 1B). **C. jejuni** exhibited aerotolerance but was not physiologically active based on the intracellular ATP levels (Figure 1C). In addition, the morphology of **C. jejuni** changed from spiral rods to coccoid forms under aerobic conditions (Figure 1D). A previous study demonstrated that **C. jejuni** is able to survive under prolonged exposure to aerobic stress by forming VBNC cells with a typical morphological change to coccoid forms (Rollins and Colwell, 1986). Harvey and Leach reported the formation of coccoid forms of **C. jejuni** is enhanced by high oxygen tension, presumably as a result of oxidative damage, and coccoid forms of **C. jejuni** may regain normal spiral morphology following adaptation to oxidative stress (Harvey and Leach, 1998). In response to various harsh stress conditions, many bacterial species are known to enter a VBNC state with significant dwarfing in size (Oliver, 2010).
FIGURE 3 | PerR regulation of sodB in C. jejuni. (A) De-repression of sodB by a perR mutation. A perR mutation de-repressed sodB transcription, and the level of sodB transcription was completely restored by complementation. The sodB promoter activity was determined in MEMα with or without 40 μM FeSO4. The results show the standard deviations of three different experiments. Statistical analysis was performed with a Student’s t-test using GraphPad Prism 6.

Although a few stress conditions have been reported to induce a VBNC state in Campylobacter, including nutrient starvation (e.g., incubation in water), cold stress (e.g., 4°C), and organic acids (e.g., formic acid) (Rollins and Colwell, 1986; Harvey and Leach, 1998; Kassem et al., 2013), mechanisms for the VBNC formation remain largely unknown. Based on the findings in this study, C. jejuni enters a VBNC state under aerobic conditions. Compared with microaerobic conditions, interestingly, the transcriptional levels of ahpC, katA, and sodB were higher under aerobic conditions, in which the majority of C. jejuni cells were in coccoid forms (Figures 1B,D). At this stage, it is not clear whether the up-regulation of ahpC, katA, and sodB occurred in viable-and-culturalble or VBNC cells or both. However, increased expression of the antioxidant genes will alleviate oxidative stress under aerobic conditions and may contribute to the protection of C. jejuni from increased oxidative stress during the physiological transition of C. jejuni to a VBNC state under aerobic conditions.

In this study, we presented a unique regulatory mechanism of oxidative stress defense in C. jejuni that non-selectively regulates superoxide and peroxide stress via PerR. Such an integrative regulatory system of PerR will help C. jejuni to survive in oxygen-rich conditions during transmission from food to humans by allowing for effective coordination of the expression of relatively few ROS-detoxification enzymes in this microaerophilic foodborne pathogen. Future studies will include the investigation of the role of the unique stress response mechanism in the survival of C. jejuni under stress (i.e., oxygen-rich) conditions, and the interplay between PerR and other oxidative stress response regulators in C. jejuni.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fmicb.2015.00126/abstract

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