Transducer like proteins of *Campylobacter jejuni*

*Campylobacter jejuni* transducer like proteins: Chemotaxis and Beyond

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ABSTRACT

Chemotaxis, a process that mediates directional motility towards or away from chemical stimuli (chemoeffectors/ligands that can be attractants or repellents) in the environment, plays an important role in the adaptation of *Campylobacter jejuni* to disparate niches. The chemotaxis system consists of core signal transduction proteins and methyl-accepting-domain-containing Transducer like proteins (Tlps). Ligands binding to Tlps relay a signal to chemotaxis proteins in the cytoplasm which initiate a signal transduction cascade, culminating into a directional flagellar movement. Tlps facilitate substrate-specific chemotaxis in *C. jejuni*, which plays an important role in the pathogen’s adaptation, pathobiology and colonization of the chicken gastrointestinal tract. However, the role of Tlps in *C. jejuni*’s host tissue specific colonization, physiology and virulence remains not completely understood. Based on recent studies, it can be predicted that Tlps might be important targets for developing strategies to control *C. jejuni* via vaccines and antimicrobials.

Key Words

Chemotaxis, methyl accepting chemoreceptors, Tlps, colonization, chicken, motility, biofilm, organic acids, amino acids, virulence, adaptation.
CAMPYLOBACTERIOSIS: AN OVERVIEW

Infections with Campylobacter are referred to as campylobacteriosis, a usually self-limiting gastrointestinal illness in humans that is characterized by diarrhea, fever and abdominal cramps and an incubation period of 2-5 days.\(^1,2\) Campylobacter infections in humans can be associated with serious and complicated post-infectious sequelae such as Guillain Barre syndrome (GBS), immunoproliferative small intestinal disease and reactive arthritis.\(^3\) GBS is an autoimmune demyelinating polyneuritis of the peripheral nervous system, with an annual incidence of 0.4-0.6 cases per 100,000 individuals.\(^4,5\) C. jejuni infects approximately 1 million people each year\(^6\) and accounted for 22,500 cases of disability adjusted life years (DALYs) in the USA.\(^7\) In 2014, Campylobacter infections had an incidence of 13.45 for every 100,000 people, surpassing the 8.5 person target set by the Centers for Disease Control and Prevention for 2020.\(^8\) Furthermore, the incidence of Campylobacter infection increased in 2014 by 13% in comparison to 2006-2008.\(^9\) The Food and Drug Administration (FDA, USA) has placed Campylobacter species in the list of “qualifying pathogens” that are capable of posing a serious public health risk.\(^9\) Campylobacteriosis is estimated to cost about $1.7 billion in economic losses annually in the USA.\(^10\) Additionally, the incidence of campylobacteriosis in the European Union (EU) can range between 2 million to 20 million according to an EFSA (European Food Safety Authority) study.\(^11\) However, the disease is frequently underreported, suggesting that the incidence of campylobacteriosis in the USA and EU could be higher. These observations highlight the global burden of campylobacteriosis and the need for the control.

SOURCES AND TRANSMISSION OF C. JEJUNI

C. jejuni is ubiquitous, occurring in many hosts and environmental niches. This bacterium can be isolated from the intestinal tract of otherwise healthy domestic and wild animals, as well as avian species specifically, chickens and turkeys.\(^12,13\) Poultry, especially chickens are natural reservoirs of C. jejuni, which primarily inhabits chicken gastrointestinal tract with high numbers (~\(10^8\) Colony Forming Units (CFU)/g of cecal content).\(^14,15\) Once infected, C. jejuni rapidly spreads in commercial flocks, likely via horizontal transmission from environmental sources, farm workers, or other farmed animals to poultry houses.\(^16\) The high densities of C. jejuni in broiler gastrointestinal tract facilitate the contamination of chicken carcasses and cognate meat products during slaughter and processing.\(^17,18\) For example, an accidental leak or rupture of the intestine can result in contamination of the chicken carcass skin.\(^19\) C. jejuni can persist and grow on chicken skin, even in a controlled atmosphere package at room temperature.\(^20,21\) The increase in demand on and consumption of poultry meat makes them a major source of human infections in developed countries.\(^22\) A significant portion of campylobacteriosis cases in humans have been associated with the consumption and handling of chicken meat contaminated with C. jejuni.\(^23\) C. jejuni is also harbored in the intestinal tract of healthy cattle with a prevalence rate of 0-80%.\(^24\) Consequently, the consumption of raw milk cross-contaminated by fecal matter during milking or due to contamination of an udder is a common source of C. jejuni infection in humans.\(^25,26\) Another reported source of C. jejuni infection is, consumption of untreated water or rain water.\(^27\) However, since poultry remain a predominant source for Campylobacter infections in developed countries, it is predicted that the reduction of C. jejuni loads in birds at the farm level and prior to slaughter would significantly decrease campylobacteriosis in humans.\(^28,29\) Thus, efforts have been historically focused on devising control strategies to mainly limit C. jejuni in meat producing poultry.

CHEMOTAXIS AND COLONIZATION

Effective control of C. jejuni requires a better understanding of the biology of this enteric pathogen. Despite existing genome information on different strains of C. jejuni, more studies are still needed on various colonization factors and
virulence mechanisms of this pathogen. Unlike other enteric pathogens, the relatively small genome of \textit{C. jejuni} lacks canonical virulence mechanisms like pathogenicity islands and type III secretion systems and classical stress response factors like the stationary phase sigma factor, RpoS.\textsuperscript{30} Taken together, these observations raise many questions: 1) how can \textit{C. jejuni} persist in markedly different niches such as animal hosts, farm environment, contaminated food, water, or raw milk?, 2) how can \textit{C. jejuni} transit through the acidic gastric barrier to colonize the mucus layer of the intestine in the host?, 3) and how can \textit{C. jejuni}, a fastidious organism, cope with the hostile environments in the host and the para-host milieu? To answer these questions, researchers have implicated several mechanisms and biological processes such as flagellar motility, biofilm formation, and alternative stress responses in \textit{C. jejuni}'s ability to adapt and persist in an environment and to colonize, invade and interact with host cells.\textsuperscript{31-33} In this manuscript, the potential role of chemotaxis in facilitating \textit{C. jejuni} adaptation along with cognate implications will be discussed.

The chemotaxis sensory system controls bacterial motility to introduce a swimming bias towards favorable environment or away from unfavorable conditions. Chemotaxis is mediated by a two-component regulator system (TCS), which consists of a membrane-associated histidine autokinase/ sensor and a cytoplasmic response regulator protein. TCS facilitates sensing and responding to a stimulus and thus plays an important role in the pathobiology of enteric pathogens.\textsuperscript{34} Therefore, chemotaxis has been extensively investigated in enteric pathogens such as \textit{Escherichia coli} which represents a paradigm for understanding chemotaxis in other bacteria, including \textit{C. jejuni}.\textsuperscript{35} \textit{C. jejuni} is chemotactic towards many components of the host intestinal mucus layer such as mucin, amino acids and organic acids and that flagellar motility in this pathogen facilitate host colonization.\textsuperscript{36} A recent study showed that chemotaxis is an essential phenomenon that contributes positively to the potential of \textit{C. jejuni} strains to competitively colonize the chicken gastrointestinal tract.\textsuperscript{37} Therefore, it can be argued that it is essential to investigate the mechanism of chemotaxis and the components of \textit{C. jejuni} signal transduction system by drawing meaningful comparisons with systems in \textit{E. coli} and other bacteria. The genome sequence of \textit{C. jejuni} NCTC11168 revealed orthologs of chemotaxis and aerotaxis genes.\textsuperscript{30} The genome sequence also revealed genes encoding methyl accepting chemotaxis proteins also called transducer like proteins (Tlps) that sense extracellular signals or stimuli in the form of ligands and transmit these signals to the cytoplasmic core chemotaxis signal transduction (Che) proteins network.\textsuperscript{38} The Che proteins of \textit{C. jejuni} include CheA, CheB, CheR, CheW, CheV and CheY. Therefore, it appears that \textit{C. jejuni} relies heavily on an extended chemotaxis network, which suggests that this phenomenon might be critical for its adaption and success as foodborne pathogen.

\textbf{THE \textit{CAMPYLOBACTER} CHEMOTAXIS SYSTEM AND THE CHEMOSENSORY COMPLEX}

Chemotaxis fundamentally relies on a two-component system for signal transduction that is common for the different stimuli-detecting chemoreceptors (see below for discussion on Tlps) and on scaffold proteins. The two-component system consists of a membrane-associated histidine autokinase/ sensor (CheA) and a cytoplasmic response regulator protein (CheY). Both aforementioned Che proteins play a pivotal role in \textit{C. jejuni} chemotaxis. The CheA is a core signal transduction protein that undergoes autophosphorylation and transfers the phosphate group to CheY, which interacts with flagellar motor switch proteins FliM and FliN in the phosphorylated state to mediate reorientation of the bacterial cells with clockwise rotation of the flagella in response to a stimulus.\textsuperscript{35,39,40} Chemotaxis systems in \textit{Campylobacter spp.} exhibit “sensory adaptation” which is defined as the restoration to a pre-stimulus state (resetting) in the continuous presence of a stimulus (chemoeffector).\textsuperscript{41} This is brought about by two possible mechanisms: 1) the manipulation of the methylation status of methyl accepting chemotactic domains in the Tlp (Transducer Like Protein) chemoreceptors which is mediated by two enzymes, a methyltransferase CheB and methyltransferase CheR.\textsuperscript{42} 2) the competition between the scaffold proteins, CheV and CheW, which show disparate affinities to different chemoreceptors.\textsuperscript{43} CheW is thought to interact with the signaling domains of Tlps to form a of
These observations highlight a complex and elegant system that conveys the necessary...sequence analysis and...specificity...ments and growth conditions...bably detects cytosolic signals...

The genome sequence of C. jejuni NCTC11168 revealed the presence of homologs of the chemotactic pathway which includes ten putative chemotactic sensory receptors designated as transducer like proteins (Tlps). The ability of bacteria to respond to different ranges of chemical stimuli depends on its chemoreceptor repertoire(s) as well as their sensitivity and specificity towards a chemoeffector. The number and kind of chemoreceptors in bacteria vary. For example, there are 5 kinds of chemoreceptors in E. coli, 8 in the soil bacterium Sinorhizobium meliloti, 4 in H. pylori, 26 in P. aeruginosa, 13 in Rhodobacter sphaeroides and 45 in V. cholerae. This variation has been attributed to the complexity in bacterial lifestyle and their ability to adapt to different environments and growth conditions. Furthermore, ternary core signaling complexes (chemoreceptors-CheA-CheW) form cooperative clusters that include teams of chemoreceptors in order to enhance CheA activity, amplify the chemotactic signal and increase the sensitivity to a stimulus. Therefore, a complex chemotactic response is possibly dictated by inter-connectivity and cooperation between comingled chemoreceptor clusters. This conveys a remarkable adaptation potential and finely attunes the bacterial cell to its environment.

As mentioned earlier, chemotactic signals in bacteria are detected by dedicated groups of transmembrane chemoreceptors that are referred to as Transducer Like Proteins (Tlps). The ability of bacteria to respond to different ranges of chemical stimuli depends on its chemoreceptor repertoire(s) as well as their sensitivity and specificity towards a chemoeffector. The number and kind of chemoreceptors in bacteria vary. For example, there are 5 kinds of chemoreceptors in E. coli, 8 in the soil bacterium Sinorhizobium meliloti, 4 in H. pylori, 26 in P. aeruginosa, 13 in Rhodobacter sphaeroides and 45 in V. cholerae. This variation has been attributed to the complexity in bacterial lifestyle and their ability to adapt to different environments and growth conditions. Furthermore, ternary core signaling complexes (chemoreceptors-CheA-CheW) form cooperative clusters that include teams of chemoreceptors in order to enhance CheA activity, amplify the chemotactic signal and increase the sensitivity to a stimulus. Therefore, a complex chemotactic response is possibly dictated by inter-connectivity and cooperation between comingled chemoreceptor clusters. This conveys a remarkable adaptation potential and finely attunes the bacterial cell to its environment.

The genome sequence of C. jejuni NCTC11168 revealed the presence of homologs of the chemotactic pathway which includes ten putative chemotactic sensory receptors designated as transducer like proteins (Tlps) and two aerotaxis receptors. C. jejuni Tlps have been classified into three groups (A-C) based on sequence analysis and structural homology (Figure 1). The group A Tlps (Tlp1, 2, 3, 4, 7 and 10) possess two membrane spanning transmembrane domains, a periplasmic ligand binding domain and a cytoplasmic signaling domain. Tlp9 (CetA) is the only group B Tlp, which along with CetB constitutes the bipartite energy taxis system in C. jejuni. Tlps of group C (Tlp5, 6 and 8) possess a single cytoplasmic signaling domain, and probably detects cytosolic signals. C. jejuni was shown to be chemotactic towards L-fucose, L-aspartate, L-cysteine, L-glutamate, L-serine, organic acids (pyruvate, succinate, fumarate, citrate, malate, and alpha-ketoglutarate), bile (beef, chicken, and oxgall) and mucin (bovine gallbladder and hog gastric). Taken together, the aforementioned potential adaptations associated with chemotaxis might be essential in facilitating C. jejuni to persist in diverse niches. C. jejuni Tlps are discussed below. Tlp5 will not be included in the discussion because a tlp5 mutant in C. jejuni could not be generated and its contributions, if any, to the adaptation of this pathogen could not be assessed.

Tlp1
Tlp1 is a group A chemoreceptor involved in sensing aspartate via specific interaction between the sensory domains of Tlp1 and aspartate. After binding to aspartate, Tlp1, interacts with the scaffolding protein CheV to relay the signal to CheA. The Tlp1 signaling domain interacts with both CheV and CheW but has a greater preference for CheV. A recent crystallographic analysis revealed that sensing aspartate is indirect with the involvement of an unidentified periplasmic binding protein. The crystal structure also revealed the presence of a periplasmic Per-Arnt-Sim (PAS) sensing domain with no ligand binding pockets or consensus motifs for amino acid recognition. The cytoplasmic domain of this chemoreceptor shows 47% similarity to the cytoplasmic domain of the Tar receptor of E. coli and is the most conserved Tlp in Campylobacter spp. A C. jejuni tlp1 deletion mutant showed increased swarming motility and a run-biased phenotype and decreased chemotaxis towards aspartate. A tlp1 mutant in C. jejuni NCTC11168-O showed an increased ability to adhere to and invade human epithelial (Caco-2) cells in vitro. However tlp1 mutants...
in *C. jejuni* NCTC11168-O and a variant strain (NCTC11168) were defective in colonization of the chicken gastrointestinal tract, possibly due to the decreased sensing of aspartate, an important source of energy for *C. jejuni*. Furthermore, another study showed that Tlp1 was not required for colonization by the highly invasive strain, *C. jejuni* 81-176. Therefore, the impact of Tlp1 might depend on the host and the *C. jejuni* strain under study. If so, this serves as an indication of *C. jejuni* adaptation capabilities that might be associated with Tlps.

**Tlp3**

Tlp3, another group A Tlp, shows homology to signaling domains in *E. coli* and *H. pylori* chemoreceptors. Interestingly, the Tlp3 can bind to different chemoattractants and chemorepellents, including isoleucine, aspartate, purine, malic acid, fumaric acid, and lysine, glucosamine, succinic acid, arginine and thiamine, respectively. Therefore, renaming the Tlp3 receptor to *Campylobacter* receptor for Multiple Ligands was proposed. Here, it also appears that both Tlp1 and Tlp3 play a role in mediating chemotaxis towards aspartate. This suggests that different Tlps might have overlapping (redundant)/cooperative chemotactic functions towards important substrates, probably enhancing the competitiveness of *C. jejuni* and its survival. Tlp3 also mediates chemotaxis to sodium deoxycholate or bile which is essential for *C. jejuni*’s successful jejunal colonization of mice. The tlp3 also plays a role in motility, autoagglutination and biofilm formation, because a tlp3 mutant exhibited decreased motility but increased autoagglutination and biofilm formation. Notably, the motility defects were not attributed to any genes involved in flagellar development and function. Additionally, tlp3 is essential for invasion and adherence of Caco-2 cells but did not affect *C. jejuni*’s colonization of the avian gut.

Variations in Tlp3 have been observed between *C. jejuni* strains. The *C. jejuni* 81-176 Tlp3 homologue has a naturally occurring mutation. The CJJ81176_1548 and CJJ81176_1549 encode the periplasmic and cytoplasmic domains of Tlp3, respectively. There is a nucleotide deletion in the sequence of CJJ81176_1548 at position 1467624 (A) in the genome, consequently changing the reading frame of the transmembrane and cytoplasmic domains (CJJ81176_1549) and resulting in incorrect translation and production of a non-functional Tlp3 protein in *C. jejuni* 81-176. There are additional mutations in the periplasmic and cytoplasmic domains with several intervening stop codons. Based on this information and previous reports, a functional Tlp3 seems to be absent in *C. jejuni* 81-176. A recent study on the expression of *tlp* genes in different *C. jejuni* strains also pointed out that *tlp3* expression was absent in *C. jejuni* 81-176 strain. It might be important to note that a functional Tlp3 and its role in aspartate chemotaxis might explain why *tlp1* mutants resulted in different colonization phenotypes in different strains.

**Tlp7**

Tlp7 is another well characterized chemoreceptor of *C. jejuni*. It is the most highly expressed chemoreceptor proteins in tested *C. jejuni* strains. The Tlp7 is encoded by two genes in *C. jejuni* NCTC11168 (cj0952c-cj0951c). In contrast, in *C. jejuni* 81-176 and 81116 strains the corresponding protein is encoded by only one gene that covers the transmembrane domain, the HAMP (found in Histidine kinases, Adenylate cyclases, Methyl accepting proteins and Phosphatases) domain as well as the MCP (Methyl-accepting Chemotaxis receptor Protein) signal domain. Therefore, Tlp7 in *C. jejuni* NCTC11168 might be translated as two separate proteins and not as a single chemoreceptor.

Tlp7 was identified to be a sensor for chemotaxis towards formate, which was notable because formate is a primary energy source and defects in formate metabolism adversely affect important survival phenotypes in *C. jejuni*. However, the utilization of formate by *C. jejuni* was unaffected by the absence of Tlp7. Furthermore, *tlp7* was essential for motility and invasion of host cells in vitro, but it did not appear to impact colonization of the chicken cecum.
Other Tlps (Tlp2, Tlp4, Tlp6 and Tlp10)

Tlp2, 4 and 10 belong to Group A Tlps, whereas Tlp6 belongs to group C proteins that possess cytoplasmic signaling domains but lack the transmembrane and periplasmic binding domain. The group C Tlp receptors of C. jejuni are relatively less understood in comparison to other chemoreceptors. Recent studies indicated that Tlp6 (Group C) and Tlp10 (Group A) are involved in chemotaxis towards aspartate and glutamate.\textsuperscript{60,72} This further corroborated that heterologous chemoreceptors can cooperate/ overlap to mediate chemotaxis toward a particular substrate in C. jejuni similar to other bacteria such as S. meliloti and E. coli.\textsuperscript{67,73,74} Tlps1, 3 and 10 were identified as chemoreceptors for aspartate, a redundancy/ overlap that suggests that chemotaxis towards aspartate might have essential implications for C. jejuni survival and adaptation.

Chemotaxis substrates can act as carbon or nitrogen sources (such as sugars, amino acids, Krebs cycle intermediates) or compounds that function as electron acceptors like oxygen, nitrate, and fumarate.\textsuperscript{75} Interestingly, Tlp6 and 10 were involved in chemotaxis towards TCA cycle organic acids such as isocitrate, succinate, propionate, and fumarate.\textsuperscript{60} The above observations corroborate that Tlps moderate chemotaxis towards a favorable environment with an optimum concentration of metabolites that affect the energy status of the bacteria.\textsuperscript{76} This clearly bestows a competitive advantage and facilities the survival and persistence of C. jejuni in a given environment.

The group A Tlps, Tlp3 and Tlp4, were similary essential for mediating chemotaxis towards sodium deoxycholate (a bile component).\textsuperscript{65} However, the Tlp4 extracellular ligand binding domain is not similar to that of Tlp3. This suggested that the Tlp4, in comparison to Tlp3, may be involved in mediating chemotaxis towards different or additional substrates. A similar observation was noted for Tlp2 (another group A Tlp). Indeed, it appears that Tlp2 plays an indirect role in mediating chemotaxis towards iron and inorganic phosphate (Chandrashekar et al, unpublished data), two very important factors in maintaining cellular homeostasis and in facilitating diverse essential functions.\textsuperscript{77,78} In P. aeruginosa, inorganic phosphate (Pi) is a chemoattractant and chemotaxis towards Pi is mediated through two chemotaxis transducers, designated CtpH and CtpL.\textsuperscript{79} CtpH was required for chemotaxis at a higher Pi concentration, while CtpL senses lower Pi concentrations. The ctpL was induced under Pi limited conditions and controlled by the phosphate (Pho) regulon.\textsuperscript{80} In C. jejuni, it remains unclear if chemotaxis towards these substrates indicates interaction with the Pho or iron uptake (Fur) regulons. Nevertheless, the vital importance of these two regulons and associated prospects further elevate Tlps to potentially central roles in facilitating the survival and adaptation of C. jejuni.

Tlp8 and Tlp9: Tlps that are involved in energy taxis

Energy taxis is one of the primary forms of environmental navigation in C. jejuni.\textsuperscript{58} Studies on C. jejuni strain 81-176 and NCTC 11168 identified two membrane associated chemotaxis transducers; CetA and CetB. The CetAB system constitutes the bipartite energy taxis system in C. jejuni.\textsuperscript{58,61} It is comprised of two co-transcribed ORFs which encode a membrane-bound methyl-accepting-domain-containing protein and cytoplasmic PAS-domain protein, CetA (Tlp9) and CetB (Aer2), respectively.\textsuperscript{81} Deletion of cetA and B in C. jejuni 81-176 strain resulted in decreased motility in agar plates supplemented with fumarate and pyruvate.\textsuperscript{61} Furthermore, a recent study also identified two additional genes involved in C. jejuni energy taxis, the cetC (aer1) and cetZ (tlp 8). CetC functions in concert with CetB to form functional sensing complexes with CetA. CetA but not CetB contributed to host cell invasion; however, both these proteins did not affect chicken colonization.\textsuperscript{66,82} Compared to the CetAB proteins, CetZ has two PAS domains and an methyl-accepting signal domain and has an antagonistic effect on energy taxis.\textsuperscript{83} Additionally, the CetZ (Tlp8) mutant was shown to be defective in biofilm formation under microaerophilic conditions and exhibited increased motility in semi-solid agar.\textsuperscript{60} BLAST analysis of Tlp8 revealed a 41% identity with BdlA protein of P. aeruginosa. BdlA is a putative methyl-accepting-domain-containing protein which mediates biofilm dispersion in P. aeruginosa, a motility
independent phenotype.\textsuperscript{84} However, unlike BdlA, Tlp8 doesn’t contribute to biofilm shedding.\textsuperscript{60} Overall, these observations highlight potential complex interactions between Tlps, energy/ nutrient sensing, motility, and biofilm formation that influence the pathobiology of \textit{C. jejuni}.

**TLP FUNCTIONS BEYOND CHEMOTAXIS**

Chemosensory systems in bacteria are classified functionally into those regulating flagellar motility, type-IV pili based motility, and alternative cellular functions (ACF).\textsuperscript{44} The ACF signaling pathways are known to regulate cellular developments, biofilm formation and other diverse processes.\textsuperscript{85,86} For example, the ACF pathways in \textit{P. aeruginosa} control biofilm formation and virulence.\textsuperscript{86,87} Also, BdlA, senses environmental cues to trigger biofilm dispersion in \textit{P. aeruginosa}.\textsuperscript{84} Despite the involvement of chemotaxis transducers in ACFs, the specific signals or environmental cues that trigger these pathways are not defined yet.

Studies in important pathogens such as \textit{V. cholerae} have described an essential role for Tlps in virulence and pathogenesis. Flagellar mediated chemotaxis contributes to \textit{V. cholerae} colonization and infectivity, enabling this enteric pathogen to colonize the lower intestinal tract.\textsuperscript{88} Specifically, TcpI and AcfB, two \textit{V. cholerae} chemotaxis transducers located within the \textit{Vibrio} Pathogenicity Island, contribute to location specific intestinal colonization and to motility. Furthermore, \textit{V. cholerae} taxis towards multiple amino acids (asparagine, arginine, glutamate, and serine) is mediated by Mlp24 (MpcX), which is required for the expression of genes encoding the cholera toxin (CT) and the stimulation of virulence determinants controlled by the ToxR regulon.\textsuperscript{89,90}

Chemotaxis is also a key contributor to \textit{H. pylori}'s virulence, where it is essential for: 1) establishing infection, 2) achieving high infectivity, 3) maintaining infection and 4) affecting localization within the stomach in a mouse model of infection.\textsuperscript{91} \textit{H. pylori} chemotaxis mediators, TlpA and C, promote colonization of the stomach in animal models.\textsuperscript{92,93} Furthermore, TlpB is important for pH taxis and sensing AI-2 (the quorum sensing molecule), while TlpD, an energy sensor, is also important for persistent \textit{H. pylori} infections and colonization in the stomach.\textsuperscript{94-99}

Recent studies have indicated that Gram negative bacteria utilize chemosensory signal transduction systems to counter environmental stress.\textsuperscript{100} Consequently, the aforementioned studies on several important bacterial pathogens suggest a far reaching impact for Tlps that affects survival and virulence mechanisms. This was corroborated in \textit{C. jejuni}, where studies have shown that Tlps play a role in important cellular functions. For example, in-vitro studies on Tlp1, Tlp3, Tlp4, and Tlp10 of \textit{C. jejuni} NCTC11168 showed that they play a role in invasion of human intestinal epithelial and chicken embryo cells.\textsuperscript{56,70} The \textit{tlp8} and \textit{tlp9} deletion mutants of \textit{C. jejuni} 81-176 were defective in invasion of INT407 cells.\textsuperscript{60,82} Considering that a \textit{Atlp8} (CetZ) mutant was defective in biofilm formation despite exhibiting an increased motility, TlpB might play a role in virulence and biofilm formation through flagella independent mechanisms.\textsuperscript{60} The hypermotility of the \textit{Atlp8} mutant might favor randomly detecting energy, compensating for the impairment of this chemoreceptor.\textsuperscript{60}

Tlps contribute to differential colonization of \textit{C. jejuni} in different sections of the chicken gastrointestinal tract (cecum, jejunum, and duodenum). For example, Tlp4 and Tlp10 (DocB) affected cecal colonization by \textit{C. jejuni}.\textsuperscript{60,66} Specifically, a \textit{tlp10} deletion mutant was defective in colonization of the chicken gastrointestinal tract, with undetectable levels of the mutant in the proximal small intestines and 10 to 100 fold reductions in the large intestines.\textsuperscript{60} The \textit{Atlp6} and 10 mutants also colonized differently in the duodenum and the jejunum.\textsuperscript{60}

Collectively, the evidence discussed above might indicate that the chemotaxis system in \textit{C. jejuni} have evolved to sense substrates that might commonly be associated with the gastrointestinal tract of its host(s), a preferred niche.
for this pathogen. This is in turn suggest that there is a direct or indirect link between the chemotaxis system and factors/functions that allow C. jejuni to survive and persist in that niche. For example, sensing certain substrates might be an incentive to form biofilms, modulate motility, and/or resist stress and minimize energy expenditure both in the host and parahost niches. However, this exciting prospect requires a significant amount of analysis to establish a clear relationship between the differences in specific nutrient availability for C. jejuni and the colonization site or niche. Nevertheless, this knowledge will shed an unprecedented light on the workings and adaptations of an important and intriguing pathogen.

CONCLUSIONS AND FUTURE PROSPECTS

Here, we highlighted the role of Tlps in chemotaxis and host adaptation of C. jejuni, an important foodborne pathogen. These chemoreceptors also appear to affect functions other than nutrient sensing such as biofilm formation, motility, and host colonization. Based on the available literature, it is clear that the Tlps are important in the biology of C. jejuni and its ability to respond to both favorable and unfavorable cues in its environment. Tlps are likely integral for initiating many complex interactions between different pathways to favor the survival and adaptation of C. jejuni in a given niche. This can be gleaned from the far reaching implications associated with impairing the chemotaxis system in C. jejuni. A prime example is the impact on C. jejuni’s colonization of the chicken gastrointestinal tract. The latter is a rich source of substrates, and a nutrient sensing mechanism (chemotaxis) provides C. jejuni with a competitive advantage to colonize this niche. For example, fumarate, which acts as an alternate electron acceptor in an oxygen limited environment, is found in the intestine where C. jejuni favors fumarate respiration. Similarly, the availability of free amino acids and organic acids, produced by intestinal microbiota contributes to rendering the environment favorable for C. jejuni colonization. Therefore, identification of chemoreceptors specifically sensing ligands such as fumarate or amino acids (e.g. aspartate, serine, and glutamate) will aid in targeting C. jejuni colonization of the avian gut. Furthermore, exploring the interaction of chemoreceptors with other regulatory pathways that contribute to C. jejuni host adaptation might identify novel mechanisms. Of particular interest is the role of Tlps in survival mechanisms such as biofilm formation and resistance to different stresses. In this regard there are many speculative questions that remain unanswered. For example, 1) could nutrient sensing contribute to a shift from a motile to sessile phenotype, promoting the establishment of biofilm? 2) Alternatively, could the Tlps indirectly initiate the dispersal of C. jejuni biofilms in response to an environmental cue? Furthermore, chemotaxis towards inorganic substrates has not received equal attention as compared to other substrates. This might open new frontiers in terms of the understanding of the biology of C. jejuni. For example, could sensing of inorganic substrates such as iron be associated with enhancing resistance to oxidative stress, given that free iron can contribute the production of lethal hydroxyl radicals (the Fenton reaction)? Iron is also a component of the Fe-S clusters of metalloproteins that have various cellular functions, which opens up staggering possibilities. Additionally, chemotaxis towards phosphate harbors much potential. For example, the metabolism of inorganic polyphosphate has been associated with pleiotropic phenotypes and regulatory functions in C. jejuni. All these possibilities and many others and cognate cellular mechanisms remain to be fully investigated. Antibiotic-resistant C. jejuni strains are increasing, which limits the efficacy of antimicrobial therapy and there are currently no vaccines commercially available against this pathogen. Therefore, unravelling the functions of chemoreceptor proteins holds great promise for developing novel drugs or vaccines that selectively target this enteric pathogen.

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Conflict of Interest Statements
The authors declare no conflict of interest.
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Figure 1: Domain architecture of chemoreceptors and chemotaxis proteins of *Campylobacter jejuni* 81-176 (in order of their location in the *C. jejuni* genome annotations) based on the Pfam (Pfam 27.0, March 2013; http://pfam.sanger.ac.uk/) and SMART (http://smart.embl-heidelberg.de/) analysis, with conserved domains represented in identically shaded regions. The transmembrane domains are abbreviated as Tm. Tar and Cache acronyms are derived from the proteins, prokaryotic aspartate receptor and animal Ca\(^{2+}\) channel subunits, respectively. The PAS domain was named after the period circadian protein –Per, the aryl hydrocarbon receptor nuclear translocator –AHR and the single-minded protein –Sim. The HAMP domain is found in Histidine kinases, Adenylate cyclases, Methyl-accepting proteins and Phosphatases. MCP stands for methyl-accepting chemotaxis receptor protein.

| Tmp | Tmp Class | SMART domain structure | Amino acids |
|-----|-----------|------------------------|-------------|
| 10  | A         |                        | 584         |
| 2   | A         |                        | 659         |
| 4   | A         |                        | 665         |
| 6   | C         |                        | 365         |
| 7   | A         |                        | 530         |
| 8   | C         |                        | 429         |
| 9   | B         |                        | 459         |
| 1   | A         |                        | 700         |
| 3   | A         |                        | 293         |
| 5   | C         |                        | 236         |

![Diagram showing domain architecture](image-url)