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The role of chemotaxis during *Campylobacter jejuni* colonisation and pathogenesis

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Campylobacter jejuni is a ubiquitous gastrointestinal pathogen, transmitted to humans from birds and animals, where *C. jejuni* is part of normal intestinal flora. In *C. jejuni*, similar to other motile bacteria, chemotaxis pathway and the array of chemosensors sense and respond to external stimuli with unique precision and sensitivity and are considered to be critical for bacterial colonisation and pathogenicity. Disruption of any component of the signal transduction pathway consisting of receptor-CheA/CheW-CheY-flagella cascade, the signal adaptation system, and even a loss of a single chemosensory receptor, dramatically reduce the ability of *C. jejuni* to colonise various animal hosts and to cause disease.

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Introduction

Chemotaxis, the ability of bacterial cells to move in response to chemical cues has long been implicated in the virulence of pathogens (reviewed in Ref. [1••]). The first step in this process is initiated by chemosensory receptors recognising chemical ligands and initiating a signal transduction cascade allowing the cell to respond by moving toward an attractant or away from a repellent. Bacterial chemosensors respond to these external stimuli with unique precision and sensitivity—a key survival trait in, for example, the search for nutrients and locating a target host cell, and as such, are considered to be critical for bacterial colonisation and pathogenicity [2–4]. Disruption of any component of the pathway, including that of a single chemosensory receptor, can reduce the ability of pathogens to colonise and cause disease [3–5].

The transduction of the chemosensory signal, initiated by the chemosensors, is governed by a two-component regulatory system involving a phospho-relay (through the receptor coupling protein CheW), from a Histidine Kinase (HK) protein CheA to a Response Regulatory (RR) protein CheY. Phosphorylated CheY interacts with the flagellar motor to alter the direction of rotation between clockwise and counterclockwise enabling movement towards an attractant or away from a repellent [6]. Methyltransferase CheR and methylesterase CheB are associated with receptor signal adaptation and allows the receptors to respond to a chemical concentration gradient. The well-researched *Escherichia coli* chemotaxis system pathway (receptor-CheA/CheW-CheY-flagella) has been used as a model to understand basis of sensory signal transduction, and previously served as a reference for the characterisation of chemotaxis in other bacteria [6]. In recent years, however, our knowledge of chemotaxis pathways has expanded to more complex scenarios in other bacteria where similar, but more complex pathways, may lead to twitching or darting motility and may be intricately interwoven with quorum sensing, biofilm formation and cytoplasmic communication [7–9].

Main text

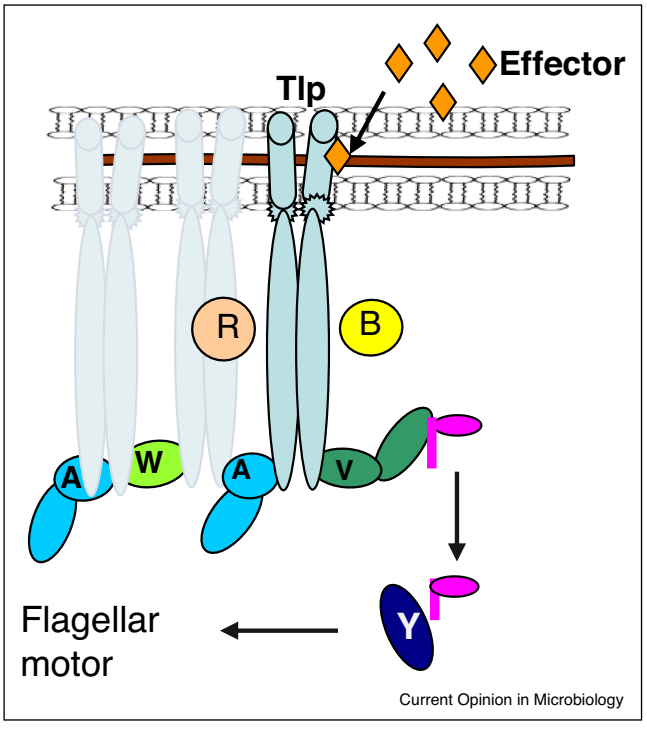
Campylobacter jejuni is recognised as the leading cause of acute human bacterial gastroenteritis worldwide [10,11]. Annual incidence of campylobacteriosis is approximated at 1–10% of the global population [12–14]. The organism is transmitted to humans from birds and animals, where *C. jejuni* is part of normal flora [14,15], with the main mode of transmission being the ingestion of contaminated food or water [16,17]. Clinical features of *Campylobacter* enteritis in humans can range from asymptomatic to acute gastrointestinal illness characterised by watery or bloody inflammatory diarrhoea [18,19]. Approximately 10% of the world's population is estimated to suffer from campylobacteriosis annually with ~10% of victims requiring to be medically treated or hospitalised (WHO) resulting in a significant health and economic burden [20]. In addition, infection with *C. jejuni* can lead to other complications such as meningitis, urinary tract infections, bacteraemia and autoimmune neuroparalysis [21,22].

Motility and chemotaxis have long been implicated in host colonisation and pathogenicity of *C. jejuni* [23,24] and as a study organism, *C. jejuni* allows a unique perspective into the role of chemotaxis in the lifecycle of infectios bacteria. It is able to colonise multiple hosts, as a commensal in avians and livestock animals, and as a pathogen

in humans, and it is ubiquitously persistent in the environment. Therefore, the bacteria has at least three niches that it has to traverse: intestines of warm blooded animals, intestines of birds and environmental niches such as water reservoirs, streams and lakes. The diverse chemotactic responses that this organism can produce to guide its directed motility are, therefore, likely to be an important mechanism involved in both host and environmental survival. It had, in fact, been demonstrated that *C. jejuni* strains modulate expression of their chemosensory receptors according to the specific host and environment [25].

C. jejuni encodes a single chemosensory pathway relaying signal through 11 sensory receptors [26,27]. Some of the other proteins involved in the chemotaxis signalling pathway are single domain proteins, similar to those found in *E. coli*, such as CheY and CheW, and there are a few that are not found in *E. coli*, but are common to other microbes, such as CheV, a two-domain protein consisting of fused CheW and CheY-like domains. Similarly, *C. jejuni* CheA protein also has two major domains, combining a catalytic HK and a regulatory RR domains, unlike the HK only CheA protein in *E. coli* [27,28] (Figure 1). *C. jejuni* CheB is unique and lacks a CheY-like RR domain, present in other CheB proteins. The differences in functions of single and double-domain Che paralogues are yet to be fully elucidated in *C. jejuni* or other bacteria.

Figure 1



Campylobacter jejuni chemotaxis signal transduction pathway: Effector—Tlp receptor—CheV/CheW/CheA—CheY—flagellar motor; CheB and CheR—signal adaptation.
Abbreviations: Tlp, Tlp receptor; V, CheV; W, CheW; A, CheA; R, CheR; B, CheB, Y, CheY; P, phosphate.

The influence of the chemotaxis pathway on colonisation capacity and pathogenicity of the organism, is, however, becoming clear. Mutations in *C. jejuni* response regulator CheY had been shown to lead to the inability of the organism to both colonise and cause disease in a ferret model [24], and CheA mutants failed to colonise mice with limited intestinal flora [29]. It is particularly interesting to note that campylobacteria with some mutationally inactivated components of the chemotaxis signal transduction cascade, such as scaffolding proteins CheV and CheW, as well as flagella assembly genes, appeared to have an enhanced ability to invade, and rapidly migrate to subcellular space of human cells in culture [30]. It should be considered, however, that CheV and CheW mutants, able to invade through subcellular space, were not tested *in-vivo* in animal models and it is not known what affect those mutations may have on colonisation or virulence of the organism. In that context, it also needs to be considered that while CheY and CcaA(Tlp1) loss of function mutations also cause an increase in attachment and invasion of human cells in culture, they attenuate the ability of *C. jejuni* to colonise or cause disease in animal models [5,24]. The potential role of the signal adaptation proteins CheB and CheR in bacterial-host interactions of *C. jejuni* had also been investigated with both proteins being implicated in the ability of *C. jejuni* to colonise chicken caeca, as was shown for CheBR deletion. It is interesting to note that the sole deletion of CheR resulted in an increase in attachment and invasion of cultured human cells by *C. jejuni* carrying this mutation [31]. Taken together, these finding suggest that every component of the chemosensory cascade of *C. jejuni* is likely to play an important role in association with host cells and the ability to of the bacteria to colonise the host.

C. jejuni chemoreceptors, Tlps (transducer-like proteins), have also been shown to affect the ability of the organism to adhere and invade human cells in culture and to colonise and infect mammalian and avian hosts. The Tlps of *C. jejuni* are classified into three groups, A–C, based on structural similarities to chemoreceptors in other organisms [28]. The group that senses ligands external to the cell is designated as Group A, and these are called: Tlp1 (CcaA), Tlp2, Tlp3 (CcmL), Tlp4(DocC), Tlp7, Tlp10 (DocB) and recently characterised Tlp11 (CcrG) [5,28,32•,33,34]. Variants of Tlp4, Tlp12, and Tlp11, Tlp13 had also been recently described in some strains isolated from animals [35,36]. Group A receptors share a common three-domain structure with other external sensory receptors—a periplasmic sensory domain, cytoplasmic signalling domain and transmembrane domain linking the two. Group B (with membrane bound cytoplasmic signalling domain and no obvious periplasmic domain) and Group C

receptors (fully cytoplasmic receptors with a signalling domain similar to that of other receptors but with very limited ligand binding domains) Tlp5, Tlp6, Tlp8 and Tlp9 relate to energy taxis and cytoplasmic sensing [27,28].

Mutational studies of Group B and C sensors suggested that these receptors may also be important for the ability of *C. jejuni* to invade human intestinal cells in culture or to colonise chicken intestinal tract [37]. However, the study did not assess what effect the defect in either cytoplasmic or energy redox sensing may have on bacterial fitness in general. General loss of fitness can also result in reduced ability of bacteria to colonise in animal model.

Unusually, Group A receptor content can vary significantly between strains of *C. jejuni,* with some strains encoding as few as 4 and other as many as 7 Group A chemosensors. Tlp1 (CcaA), Tlp7 and Tlp10 (DocB) appear to always be present in *C. jejuni* subspecies *jejuni*, and Tlp10 can be absent in some *C. jejuni* subspecies *doilei* strains [25]. The most studied *C. jejuni* strains, NCTC11168, 81116 and 81-176 (all isolated from human patients) have 6 group A chemosensors, Tlps 1–4, 7, and 10. However, even here there is a certain level of variation: in 81-176 Tlp3 has a natural mutation, and NCTC11168 encodes Tlp7 as two peptides with a stop codon between sensory and signalling domains of the protein. If is yet to be fully elucidated how the 2 Tlp7 peptides can associate to form a functional receptor [25]. Tlp7 of *C. jejuni* strain B2, similar to that of strain 11168, occurs as two peptides and was reported to respond to formate, although it is not known if this occurs by direct sensing by Tlp7 periplasmic sensory domain or indirect sensing through an unknown periplasmic binding protein [38].

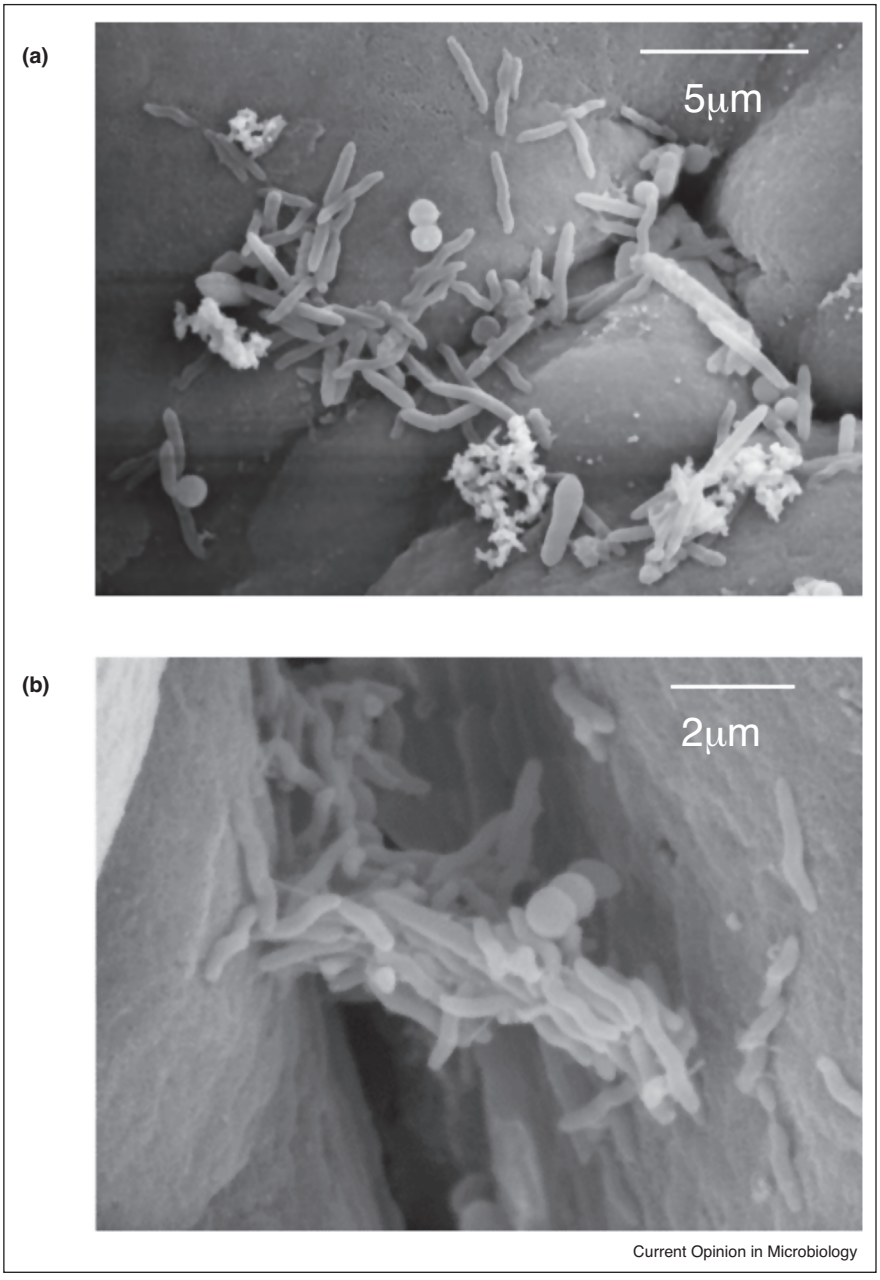
Similar to other components of chemotaxis pathway, Group A chemosensors are important for association of *C. jejuni* with human cells and for colonisation of avian and mammalian hosts. Tlp1(CcaA), the aspartate receptor, and CcrG(Tlp11), the galactose receptor were shown to be involved in the ability of *C. jejuni* 11168-O to migrate to and attach to human intestinal cells in culture, as isogenic deletion mutant strains had significantly reduced ability (by 2–4 orders of magnitude), to colonise avian and mammalian hosts [5,32•]. The loss of function Tlp1 mutant displayed a 'run' phenotypic bias, where the ability of bacteria to tumble and re-orient was affected, and enhanced the ability of the bacteria to adhere and invade human cell in culture. While the same mutation in Tlp1 was attenuating in chicken and murine models of colonisaiton, a very unusual effect was noted: the animals infected with the Tlp1 mutant showed dramatic and visually obvious pathology after 24–48 hours post infection. The chickens had gross mesenteric intestinal fat roping and the mice had clear hepatomegaly [39•]. After 5 days, these effects disappeared and bacterial numbers reduced significantly below those found in animals infected with wild type bacteria. It is possible that the 'run' hyperinvasive phenotype of the mutant enhanced its ability to rapidly transverse the intestinal wall and made the mutant bacteria available to the immune cells to a greater extent than is usual for the wild type cells, leading to greater inflammatory response and subsequent clearing.

Tlp11, the *C. jejuni* galactose receptor, was the first dCACHE_1 receptor shown to sense a sugar, galactose, a compound commonly found on mammalian cell surface, but the one that this organism cannot metabolise. *C. jejuni* cells encoding this receptor naturally, and the cells with this receptor added to their normal chemoreceptor repertoire were attracted to the HTC (human colorectal cancer cell line) cells overexpressing a cell surface mucin MUC1 to a greater extent than the campybacteria not possessing this receptor [32•]. This information allows for a postulate that the sensory machinery of *C. jejuni* is geared to sense not only the nutrients it requires to thrive, but also for the ability to sense host-specific molecules.

The three most variable *C. jejuni* chemoreceptors, Tlp3, Tlp2 and Tlp4 form a unique family of sensory proteins, paralogues occurring within the same bacterial species, and have possibly arisen through domain duplications, followed by divergent evolutionary drift. Tlp3(CcmL), Tlp2 and Tlp4 have divergent sensory domains and identical cytoplasmic signalling domains [28]. Tlp3, and Tlp4 are multiligand receptors with overlapping specificities and Tlp3 had been shown to be able to interact with multiple attractants and repellents [34,40], indicating potential redundancy or common ancestor gene, or both. Ligand specificity of Tlp2 is yet to be reported. The insertional inactivation of the multiligand receptor CcmL (Tlp3) of *C. jejuni* 11168 resulted in a 'tumble' bias phenotype and did not affect overall colonisation efficiency of the bacteria, but it did affect the mode of colonisation of the avian host, leading to production of biofilm-like micro-colonies in chicken caeca and an increased ability to produce biofilms *in vitro* (Figure 2) [34]. In addition, a double mutant in Tlp3 and Tlp4 of *C. jejuni* 11168, had been reported to be attenuated for the ability of this strain to colonise mice [40]. It is interesting to note that *C. jejuni* strain 81-176 has a natural mutation in Tlp3 and had been reported to colonise the chicken caeca in a similar manner to Tlp3 mutant of 11168 strain, and is known to be a high biofilm former [33,41]. It is yet to be determined which amino acid residues in the proposed ligand binding sites of multiligand receptors are responsible for binding the various ligands and how a single receptor is able to conduct both attractant and repellent signals to the cytoplasmic signalling domain for signal transduction.

Whole genome transposon mutagenesis (Tn), followed by screening in model animals had been employed to

Figure 2



SEM of Δtlp3 aggregating on the surface of chicken caeca.
Presence of *C. jejuni* 11168-O **(a)**, Tlp3 isogenic mutant **(b)** in a dissected portion of the chicken caeca and visualised under SEM, 5 days post infection. SEM images illustrate micro-colony formation on the surface and in the crevices of chicken caeca, and presence of extracellular polysaccharide for Tlp3 isogenic mutant of *C. jejuni* 11168-O. Scale: 2 μm.

investigate genes important for colonisation and infection. Genome wide Tn mutagenesis of *C. jejuni* 81-176 highlighted that the homologues of Tlp4 and Tlp10 (referred to in that study as DocC and DocB respectively) play a role in chick colonisaiton, as bacteria carrying the mutations in these receptors had reduced ability to colonise birds in a 2-day old chick model [33]. Furthermore, orthologues of chemosensory receptors Tlp7, Tlp3 and Tlp2 of *C. jejuni* strain M1 were similarly implicated in the ability of this strain to infect animals in gnotobiotic piglet model, following a genome wide transposon-based mutagenesis.

Overall, the analysis of the *C. jejuni* chemotaxis signal transduction pathway showed that all the pathway components examined: chemosensors, CheW/CheV and

CheA histidine kinase complex, adaptation proteins CheB and CheR and response regulator CheY are important to the ability of this organism to colonise, infect and cause disease in avian and mammalian hosts.

Conclusion

The analysis of the current state of knowledge of chemosensory pathway of *C. jejuni* demonstrates that the disruption of any component of the pathway, including that of a single chemosensory receptor, with potentially redundant specificities, has a significant deleterious effect on *C. jejuni* colonisation of avian and mammalian hosts [5,32•,34]. Full characterisation of such a subset of sensory receptors presents a unique opportunity to extend the knowledge of sensory diversity and capabilities of bacterial chemotaxis systems not only from a mechanistic and bacterial virulence, but also from an evolutionary perspective.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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