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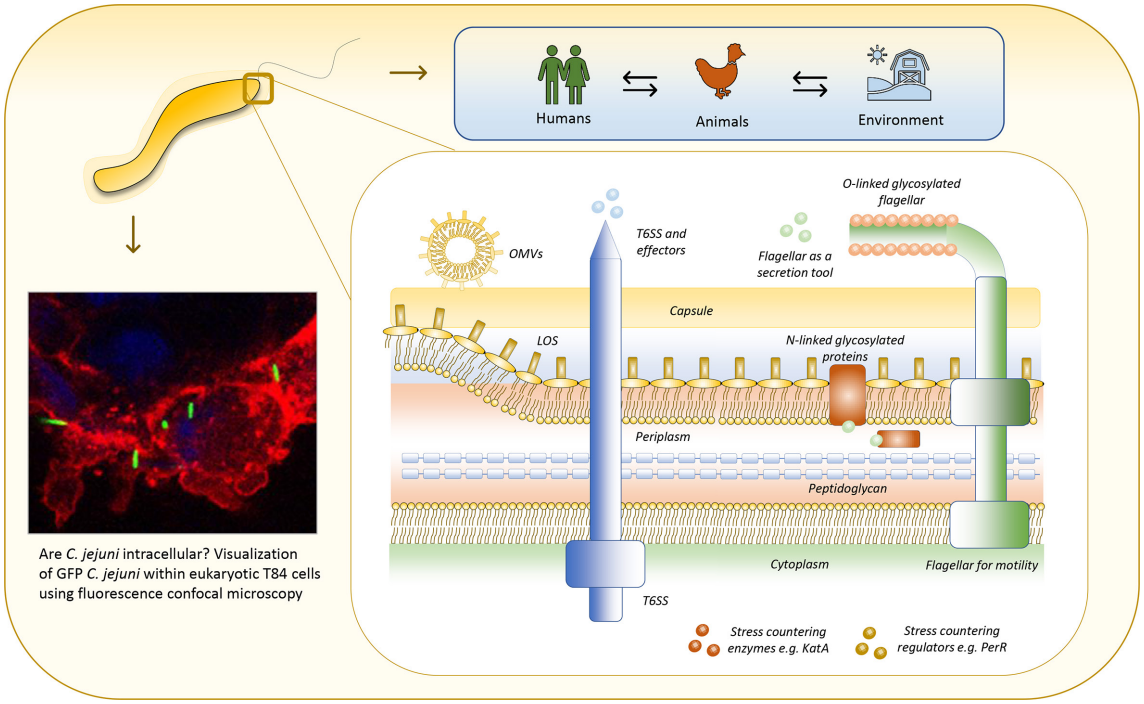
Microbe Profile: *Campylobacter jejuni* – survival instincts

Ozan Gundogdu* and Brendan W. Wren*



Graphical abstract

(Top left) *Campylobacter jejuni* model. (Top right) *C. jejuni* transmission routes between humans, animals (particularly avian species) and the environment. (Bottom left) Are *C. jejuni* intracellular? Visualization of GFP *C. jejuni* within eukaryotic T84 cells using fluorescence confocal microscopy. Live bacteria (OD_{600} of 0.1) were added and co-incubated with T84 cells for 2 h. Cells were fixed with paraformaldehyde, washed with PBS, stained and mounted. Cells were immunostained with anti-wheat germ agglutinin to indicate membranes (red) with DAPI to indicate nuclei (blue), with *C. jejuni* GFP (green) (courtesy of Dr Abdi Elmi). (Bottom right) The major factors aiding *C. jejuni* survival include stress countering enzymes and their respective regulators, type VI secretion system (T6SS), *O*- and *N*-linked glycosylation systems, capsule, lipooligosaccharide, outer membrane vesicles and the flagella for motility and secretion of effectors.

Abstract

Campylobacter jejuni is considered to be the most common bacterial cause of human gastroenteritis worldwide. *C. jejuni* can cause bloody diarrhoea, fever and abdominal pain in humans along with post-infectious sequelae such as Guillain-Barré syndrome (a paralytic autoimmune complication). *C. jejuni* infections can be fatal, particularly among young children. *C. jejuni* are distributed in most warm-blooded animals, and therefore the main route of transmission is generally foodborne, via the consumption and handling of meat products (particularly poultry). *C. jejuni* is microaerophilic and oxygen-sensitive, although it appears to be omnipresent in the environment, one of the many contradictions of *Campylobacter*.

TAXONOMY

Phylum: *Proteobacteria*; Class: *Epsilonproteobacteria*; Order: *Campylobacterales*; Family: *Campylobacteraceae*; Genus: *Campylobacter*; Species: *C. jejuni. C. jejuni* has two subspecies, *C. jejuni* subsp. *jejuni* and *C. jejuni* subsp. *doylei*. Recently, it has been suggested that the *Epsilonproteobacteria* subclass within the *Proteobacteria* may not be warranted and should be reassigned to a novel phylum [1].

PROPERTIES

Campylobacter jejuni is a Gram-negative bacterium classified as microaerophilic and capnophilic, and requires atmospheric conditions of 3–10% oxygen and 5–10% carbon dioxide for optimal growth, with a growth temperature range between 30 and 47 °C. Cells of *C. jejuni* can be curved, rod-shaped or spiral, with a size range of 0.2–0.8 µm width and 0.5–5.0 µm length, with amphitrichous flagella. The bacterium is oxidase-positive and energy is typically obtained from amino acids or tricarboxylic acid cycle intermediates rather than the utilization of carbohydrates.

GENOME

C. jejuni strain NCTC11168 was among the first bacterial genomes sequenced with an estimated size of 1.64 Mb (30.6% G+C) and 1654 predicted ORFs. This genome was later re-annotated to 1643 ORFs. The NCTC11168 genome is unusual with a lack of insertion, phage-associated and repeat sequences. However, it has a high prevalence of homopolymeric tracts, resulting in the slip-strand mispairing of genes encoding surface structures such as the capsule and the lipooligosaccharide (LOS). No type III or IV secretion systems have been identified, but a general *N*-linked glycosylation system that post-translationally modifies over 70 proteins was identified. *C. jejuni* displays extensive ongoing genetic variation, arising from intragenomic mechanisms as well as genetic exchange between strains and other species [2]. The genomic diversity and plasticity of *C. jejuni* is demonstrated with the large number of sequence types, host generalist and specialist strains. Further *C. jejuni* strains have since been sequenced from human, animal and environmental sources and have varied genotypic and phenotypic characteristics (e.g. *C. jejuni* 81-176 harbouring plasmids pVir and pTet). Recent studies have also identified an increasing number of strains with type VI secretion systems (T6SSs) [3]. However, in contrast to other enteric pathogens, relatively few genomes have been sequenced and the true global diversity and representation of the *C. jejuni* pan-genome remains to be determined.

PHYLOGENY

The *Epsilonproteobacteria* class of *Proteobacteria* consist of the renowned species *Helicobacter* and *Campylobacter*. There are currently 17 species and six subspecies assigned to the genus *Campylobacter*. The most frequently reported are *C. jejuni* (subspecies *jejuni*) and *C. coli*. The vast majority of epsilonproteobacterial species exist in deep-sea hydrothermal vents (e.g. *Sulfurimonas* species), perhaps indicating an ancient origin of the genus *Campylobacter*. These bacteria characteristically exhibit chemolithotrophy: organisms that can derive their cellular carbon from carbon dioxide, and are thus able to grow without organic compounds or light. Some deep-sea vent *Epsilonproteobacteria* also share potential virulence genes from pathogenic counterparts, e.g. CiaB and haemolysin. Interestingly, many of the deep-sea vent species have the unusual *N*-linked general protein glycosylation system first identified in *C. jejuni* NCTC11168. Thus, evolutionary links exist between important human/animal pathogens such as *Campylobacter* and *Helicobacter*, and their non-pathogenic chemolithoautotrophic deep-sea vent distant relatives.

KEY FEATURES AND DISCOVERIES

Despite specific microaerobic growth requirements [4], *C. jejuni* is ubiquitous in the ambient environment and must have genetic regulatory mechanisms to withstand aerobic stresses. *C. jejuni* possesses a range of enzymes that are involved in the breakdown of reactive oxygen species, e.g. KatA and SodB. *C. jejuni* also comprises regulators involved in the oxidative stress response such as PerR, Fur, RrpA, RrpB and CosR. Many of these regulators have dual functions and are often linked to metabolic functions such as iron homeostasis. One key attribute of *C. jejuni* aiding its survival is the ability to form and survive in biofilms and under stress to form viable but non-culturable cells.

Key structures such as LOS, capsule and flagella have been investigated with the aim of understanding *C. jejuni* survival and pathogenesis. Flagella, which are modified by an *O*-linked glycosylation system, have been hypothesized not only to play a role in motility, but may also act as a secretion system discharging effectors such as CiaB. More recently, T6SSs have been identified in an increasing number of *C. jejuni* strains and the presence of T6SSs has been associated with a response to oxidative stress [5]. *C. jejuni* produces a cytolethal distending toxin which has been reported to arrest at the G_1/S or G_2/M transition of the

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Author affiliations: [1]London School of Hygiene & Tropical Medicine, Department of Infection Biology, Faculty of Infectious & Tropical Diseases, Keppel Street, London WC1E 7HT, UK.
*Correspondence: Ozan Gundogdu, Ozan.gundogdu@lshtm.ac.uk; Brendan W. Wren, brendan.wren@lshtm.ac.uk
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Abbreviations: CCV, *Campylobacter*-containing vacuole; LOS, lipooligosaccharide; T6SS, type VI secretion system.

cell cycle, depending on the cell type. Adherence factors such as FlpA and CadF, which bind to fibronectin on epithelial cells, have also been studied. It has been reported that *C. jejuni* primarily uses a microtubule-dependent process for penetration, and once inside the host cell, exists within a *Campylobacter*-containing vacuole (CCV). *C. jejuni* is able to modify the CCV to meet its metabolic needs and also interfere with the canonical endocytic pathway, preventing *C. jejuni* killing within lysosomes [6]. Outer membrane vehicles have also been explored which can act as cargo delivery vehicles, possibly containing and delivering virulence-related proteins [7].

In summary, the lack of a convenient animal model reproducing human disease has been a major hurdle in understanding the pathogenesis of *Campylobacter* infection, with only recently new models being available [8]. Perhaps the biggest impact of *C. jejuni* research is the discovery and exploitation of the *N*-linked glycosylation system and its subsequent transfer to *Escherichia coli* cells for glycobiotechnological applications [9]. These include the development of low-cost recombinant glycoconjugate vaccines against many bacterial species, including *C. jejuni*.

OPEN QUESTIONS

Many questions remain and still perplex campylobacteriologists including:

- How can a microaerophilic organism survive and be omnipresent in the natural environment?
- How does *C. jejuni* causes disease, including diarrhoea and post-immune complications?
- Does *C. jejuni* survive intracellularly during human infection? If so what are the molecular mechanisms?
- Why are birds, particularly poultry, so susceptible to colonization by *C. jejuni?*
- How can birds tolerate trillions of *C. jejuni* cells without having overt disease, yet only 500 cells cause severe disease in human hosts?
- Why does campylobacteriosis present differently in low-income countries (watery diarrhoea) compared to high-income countries (bloody diarrhoea)?
- Has farming intensification in high-income countries led to the expansion of selective clonal lineages that are different to strains from low-income countries that often have T6SSs?

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Conflicts of interest
The authors declare that there are no conflicts of interest.

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