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PUTATIVE MECHANISMS AND BIOLOGICAL ROLE OF COCCOID FORM FORMATION IN *CAMPYLOBACTER JEJUNI*

N. Ikeda and A. V. Karlyshev*

School of Life Sciences, Faculty of Science, Engineering and Computing, Kingston University, Penrhyn Road, Kingston-upon Thames, KT1 2EE, UK

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In certain conditions *Campylobacter jejuni* cells are capable of changing their cell shape from a typically spiral to a coccoid form (CF). By similarity to other bacteria, the latter was initially considered to be a viable but non-culturable form capable of survival in unfavourable conditions. However, subsequent studies with *C. jejuni* and closely related bacteria *Helicobacter pylori* suggested that CF represents a non-viable, degenerative form. Until now, the issue on whether the CF of *C. jejuni* is viable and infective is highly controversial. Despite some preliminary experiments on characterization of CF cells, neither biochemical mechanisms nor genetic determinants involved in *C. jejuni* cell shape changes have been characterized. In this review, we highlight known molecular mechanisms and genes involved in CF formation in other bacteria. Since orthologous genes are also present in *C. jejuni*, we suggest that CF formation in these bacteria is also a regulated and genetically determined process. A possible significance of CF in the lifestyle of this important bacterial pathogen is discussed.

Keywords: *Campylobacter jejuni,* coccoid form, cell shape, peptidoglycan, viability, viable but not culturable form, stress response, cell wall

Introduction

Classification of bacteria is traditionally based on their cell shape. The names of bacterial species such as *Streptococcus*, *Staphylococcus*, *Vibrio*, etc. are based on the usual appearance of the cells under a microscope. However, bacterial cell morphology is not static. Under certain conditions such as nutrient deficiency, alleviated temperature and other stress factors, the cell shape may undergo dramatic changes.

One remarkable change is transformation from a rod or spiral form into a spherical or coccoid form (CF). CF cells of some bacteria represent dormant viable but non-culturable (VBNC) forms able to resuscitate and convert to culturable and fully infective forms. Characteristically, spiral cells of *Campylobacter* spp. (from "campylos" meaning "spiral" in Greek) are also known to be able to convert into CF *(Fig. 1)*. Whether the latter form of *Campylobacter* can be resuscitated and cause a disease is a controversial issue.

Following publication of some reports suggesting that CF of *Campylobacter* and that of the closely related bacteria *Helicobacter pylori* are just degenerative forms of these bacteria, there has been a remarkable decline in interest in this phenomenon. *Figure 2* demonstrates significant initial interest to this phenomenon as shown by a hike in a number of publications in year 1994, when it was suggested that CF represents VBNC cells with a potential to "hide and strike". Publications suggesting that CF of *Campylobacter jejuni* and *H. pylori* are simply degenerative/dead cells led to a loss of interest in such studies, and even publication of the first *C. jejuni* sequence failed to reverse the trend *(Fig. 2)*.

This review will provide a critical analysis of the current state of studies on CF of *C. jejuni*. One aim of this review is "resuscitation" of interest to a remarkable phenomenon of CF formation in *Campylobacter* by highlighting possible biochemical and genetic mechanisms of this process, and its possible role in the life style of this important pathogen.

Campylobacter: an overview

Campylobacter bacteria are known as spiral cells between 0.5 and 5 μm long and 0.2 and 0.8 μm wide, which can be uni- or bi-flagellated, with some spp. being multi-flagellated (*C. showae*) or non-motile (*C. gracilius*) [1, 2].

C. jejuni is a microaerophilic, capnophilic, thermophilic subspecies with optimal growth temperature varying from 37 °C to 42 °C. Despite fastidious growth requirements in laboratory environment, *C. jejuni* is the

*Corresponding author: Andrey V. Karlyshev, School of Life Sciences, Faculty of Science, Engineering and Computing, Kingston University, Penrhyn Road, Kingston upon Thames, KT1 2EE; UK
Phone: +44 (0)20 8417 7405; Fax: +44 (0)20 8417 7497; E-mail: a.karlyshev@kingston.ac.uk

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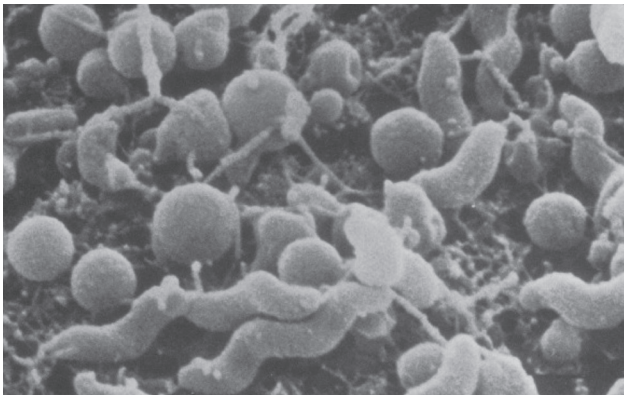

Fig. 1. Scanning electron micrographs of spiral and coccoid cells of *C. jejuni*. Reproduced from Ref. [14] (with kind permission from the publisher, American Society of Microbiology)

greatest cause of bacterial foodborne illnesses to humans in the world, more so than *Shigella* and *Salmonella* combined [3, 4]. The pathogen is transmitted by avian species including chickens, in which it is commonly present as a part of commensal microbial flora. It is not therefore surprising that infection often results from consumption of undercooked poultry products [5].

C. jejuni is the aetiological agent of Campylobacteriosis, characterized by watery or bloody diarrhoea, vomiting, nausea and fever, with reports of an infectious dose being as low as 500 organisms [6, 7]. However, due to its self-limiting nature, it is only fatal in the immuno-compromised, the very young, or the elderly. This infection can also lead to such complications as reactive arthritis, inflammatory bowel syndrome and Guillian–Barré syndrome (GBS) [8].

The rates of re ported cases of *Campylobacter*, according to HPA (Health Protection Agency, United Kingdom), are increasing every year, becoming a public health concern as well as an economic burden. Despite increased public awareness of the disease and preventative measures, the rate of reported *Campylobacter* infections in England and Wales in 2010 was 62 684, corresponding to an 8.5% annual rise [9]. In 1995, the costs of *Campylobacter*-associated diseases was estimated to cost the US economy $1.5–8 billion [10]. Because of a particular nature of the disease (usually a short-term acute form followed by a quick recovery), there is likely to be a number of under-reported cases, and so the actual economic impact of these infections is likely to be much higher than estimated.

Properties of coccoid forms

The first *Campylobacter* CF-related report available on Web of Science reference database appeared in 1982 [11]. However, it may have been known long before that, because of changes in bacterial names. For example, in 1964, CF cells were described in *Vibrio fetus* [12]. According to changes in nomenclature and bacterial classification in 1994, these bacteria were later renamed into a subspecies of Campylobacteriaceae [13].

In addition to a CF, *Campylobacter* cells may also be seen as filaments, doughnuts and straight rods [14]. For the purpose of this review, we use RF (rod form) both for rod-shaped and spiral bacteria. The RF of *C. jejuni* is considered the usual viable form found at the exponential phase of growth, whilst filaments and CF are associated with the stationary phase of growth [15]. It was suggested that transition from RF to CF occurs via an intermediate shape that resembles a "doughnut" as the cells curl to become spherical [14]. Another intermediate shape that has been seen is the "club" shape, which is characterized by localized expansions of the cell [16, 17]. However, this structure is rarely seen in *C. jejuni* electron micrographs, suggesting that the form is very short lived and may be an artefact.

Formation of the CF of *Campylobacter* is stimulated by stress conditions, which include suboptimal temperature, starvation and osmotic stress [18–20]. Coccoid cells have other characteristics besides the obvious feature of their shape. It was revealed that, despite the presence of flagella, coccoid cells of *C. jejuni* are non-motile [17, 21]. The lack of motility could be a repercussion of the morphology. The corkscrew shape allows for smoother movement within mucous membrane of the gastrointestinal tract [22, 23]. It was suggested that the non-motile nature of the CF is the result of inability of these cells to provide the energy required for flagella movement [24].

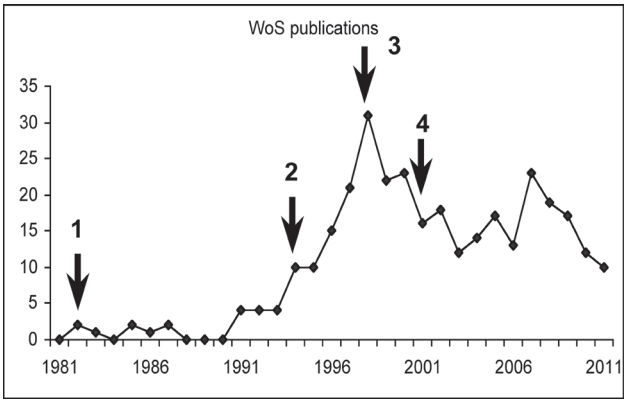

Fig. 2. Important milestones in studies of CF in *Campylobacter* and *Helicobacter* and the annual rate of relevant publications. The keyword combination "coccoid AND (*Campylobacter* OR *Helicobacter*)" was used for search of Web of Science publication database. The following time-points are marked by arrows: (1) the first mentioning of CF of *Camplobacter* spp. [11]; (2) the interest to studies of CF in these and related species received a burst after a publication, suggesting that CF are dormant but viable (potentially infective) cells [13]; (3) publication of an article suggesting that CF of *Helicobacter* is "morphologic manifestation of cell death" [47], which stimulated decline in these studies; (4) availability of the first complete *Campylobacter* genome sequence [66] had little impact on the rate of publications mentioning CF formation in these and related bacteria, with very little progress on investigation of the molecular mechanisms of this process, the biological role of which remains a mystery

Electron microscopy studies revealed that the size of the CF cells can also vary to a greater extent than that of the spiral cells [25]. Because of changes in lysozyme and ethylenediaminetetraacetic acid (EDTA) sensitivity, it was suggested that CF transition involves changes in cell wall peptidoglycan (PG) [17]. This was also supported by difference in Gram staining of CF and RF cells. Whilst the rods and spiral cells were stained typically as Gram-negative bacteria, the coccoid cells were unable to retain as much counterstain (safranin or carbol fuchsin), indicating some changes in the cell wall structure [17, 26].

The lack of structural integrity of the membranes of CF and their "leakage" were also confirmed by reduced levels of nucleic acids, as well as polypeptides, such as superoxide dismutase, when compared to the RF [17, 21]. The CF cells were found to undergo autolysis, suggesting that they may represent a degenerative form of the bacteria [18]. However, this finding contradicted with electron microscopy studies, which demonstrated no signs of autolysis of cells in CF [27].

The conflicting results may be due to different types of CF cells formed under different stress conditions. For example, CF formed under high temperature stress reveal much higher degradation of the cell wall as compared to CF induced under other conditions (described in more details in section "Temperature stress") [28]

CF and VBNC

Morphological changes to CF are coincident with the decrease in colony-forming unit (cfu) counts and were initially associated with the VBNC state [29, 30]. The VBNC state is defined as "a state of dormancy where growth ceases on bacteriological media normally used for culture of the organism yet the bacteria retain vitality with minimal activity" [26].

Formation of the VBNC cells allows bacterial survival in a dormant state in harsh conditions and is considered to be of great importance for many bacteria [31]. A link between CF and the VBNC form was noticed in a variety of microorganisms, for example, *Actinomyces radicidentis* [32], *V. vulnificus* [33], *V. cholera* [34], *Mycobacterium smegmatis* [35] and *Salmonella typhimurium* [36]. Association of CF with the VBNC state of *C. jejuni* would help to explain the incidences of infections by *Campylobacter* with no discernable environmental source [37].

According to one study, CF retained viability as judged by cell membrane integrity [29]. Despite a decrease in culturability, the amount of adenosine triphosphate (ATP) within the cells was constant for 3 weeks, which could be indicative of potential viability [29]. However, the relationship between CF and VBNC states for these bacteria has become more ambiguous after a discovery of non-coccoid VBNC cells [38]. Formation of spiral VBNC cells has been confirmed at lower temperatures [30, 39]. It was also reported that killed cells with damaged membranes retained spiral morphology, whereas cells in CF retained membrane integrity [40]. However, the issue of "viability" is controversial, as different assays and criteria for bacterial viability are employed in different labs.

There have been reports of reversion of VBNC forms into culturable forms after acid treatment [41]. In addition, according to some studies using animal models of infection, the VBNC CF of *C. jejuni* was suggested to be able to revert into fully infectious forms [42–44]. However, it was noticed that some of these results were also controversial due to irreproducibility of the data [45].

CF formation in *C. jejuni* was accompanied by a significant reduction in the level of protein synthesis, thus supporting the argument in favour of degeneracy [21, 30, 46]. In addition, CF formation in the closely related bacteria *H. pylori* was considered as a sign of programmed cell death (PCD) [47–49]. However, specific changes in the protein profile of *H. pylori* concomitant with accumulation of specific proteins during conversion into CF suggested biochemical processes different from a simple decay-like "degenerative" mechanism [49].

The VBNC state and CFF (CF formation) are clearly distinct though related events in the lifestyle of *Campylobacter* and other bacteria. It is possible that the VBNC state may induce CF formation. However, being in the CF state may not necessarily be an indication of a VBNC state. Conflicting results regarding viability of CF and RF may depend on the different stages and conditions under which these forms are generated and observed, as well as on the methods used in these studies [46].

Stimuli in the induction of coccoid form formation

As stated previously, transformation into CF is stimulated by various stress-inducing factors. The respective mechanisms of CF formation my also be different, and thus the nature and properties of CFs observed under these conditions may also vary, which partly explains the reason for contradictory results obtained with CF of *C. jejuni* in different labs.

Temperature stress

Depending on temperature, both the rate of CF formation and the type of coccoid cells formed may be remarkably different. In particular, fatty acid composition of CF cells formed at 4 and 12 °C was different from that obtained at 25 °C [46]. There is also variation in the level of biochemical activity at temperatures below 30 °C [50]. The rate of transition to CF in both *C. coli* and *C. jejuni* was higher at 37 °C compared to that at 10, 20 and 4 °C [30, 51, 52].

The effect of low temperatures on bacterial viability and the transition to CF was also found to be strain dependent [39, 53]. Types of CF formed at different temperatures may have physiological importance taking into account the conditions *C. jejuni* encounters during its life cycle, such as 37 °C within the human host compared to lower temperatures bacteria may encounter in the environ-

ment or at 4 °C used for storage of poultry and other potential food reservoirs [51].

Oxidative stress

Exposure to oxygen is a well-known factor inducting CFF in *Campylobacter* [12, 17, 21, 54]. Oxidative stress results from the effect of reactive oxygen species (ROS), such as superoxides and hydrogen peroxide. *C. jejuni* CF cells formed as a result of prolonged exposure to atmospheric oxygen retained membrane integrity, suggesting their potential viability [40]. Conversely, other studies demonstrated high level of cell membrane damage in CF formed in these conditions [55].

In certain conditions, *C. jejuni* was shown to be able to grow at ambient atmosphere. This is thought to be a result of either adaptation of the bacterium to aerobic environment or to growth media containing oxygen scavengers, for example, blood and pyruvate [3, 52, 56, 57]. The presence of these oxygen scavengers can also have an effect on the transformation to CF [52]. CF induced at 37 °C under anaerobic condition appeared uniformly spherical unlike the irregular shaped coccoid cells formed under microaerophilic and aerobic conditions [58].

In a biofilm, bacteria form layers differentially exposed to atmospheric oxygen, with the bacteria in the outer layer mostly affected and those in the inner layer protected from adverse effect of oxidative stress. The monospecies biofilms of *C. jejuni* have been shown to increase resistance to environmental stresses [59]. Bacterial cells in biofilms formed by *Campylobacter* are heterogeneous in morphology, with approximately equal ratio of CF and RF in *C. jejuni*, but predominately CF or RF in *C. mucosalis* and *C. curvus*, respectively [60]. It was suggested that CFs in biofilms of *C. jejuni* may have a supportive role by forming a layer of coccoid cells as a means of protecting the viable spiral form from the hostile environment [61].

The extracellular matrix of *C. jejuni* biofilms was found to contain DNA [62]. However, how the DNA becomes a part of the biofilm is still questioned, with two options being active DNA secretion or its passive release from cells with damaged membranes. In *Pseudomonas aeruginosa*, DNA is released into the biofilm matrix via small vesicles without cell lysis [63, 64]. However, in *C. jejuni*, it is possible that the exogenous DNA for the biofilm matrix could be contributed by CF forms as opposed to vesicles. The presence of DNA in biofilms along with the various states of permeability CF formation membranes could provide great insight into the lifestyle of *Campylobacter* and reveal the potential biological role of the CF formation.

Starvation and stationary phase

Entry into the stationary phase in many bacteria is accompanied by biochemical and morphological changes enabling the cells to increase resistance to inhospitable environments [65]. In *Campylobacter*, transition of RF to CF is a common observation in the stationary phase of growth due to stress caused by the reduction in nutrients and increase in toxic products [25, 37]. Stress response in these bacteria does not involve the "traditional" RpoS-mediated stationary phase response found in most other Gram-negative bacteria [22, 66, 67].

Programmed cell death and stringent response

The theory of bacterial PCD is a relatively new concept [68]. A link between CF and PCD in *H. pylori* has been postulated, as morphology change was coincident with a decline in viability and loss of membrane integrity [48]. A particular way of induction of bacterial PCD is via toxin–antitoxin system modules, also known as "addiction modules". An example of this is the *mazEF* gene pair in *Escherichia coli* [69]. The toxin–antitoxin systems consist of a stable toxin and unstable antitoxin that prevents the action of a toxin. The toxin–antitoxin system can be triggered by DNA damage or other stress effects, resulting in the unstable antitoxin being degraded at a faster rate compared to the stable toxin. Accumulation of the latter would result in cell death. Systems similar to the MazEF module of *E. coli* were also described in other organisms [70].

Although no *Campylobacter* "toxin–antitoxin" systems have been described, expression of *E. coli mazF*/*mazE* genes was found to be regulated by 3′,5′-bispyrophosphate (ppGpp) [69], which also plays a role in CF formation in *Campylobacter* (see below). This could also lead to speculation of the potential of PCD within *C. jejuni* biofilms. If the biological role of CF within biofilm is to maintain and create a microenvironment providing protection from external stresses and enabling the survival of a subpopulation of viable cells, PCD would likely be necessary.

Stringent response is defined as "a global stress response that alters gene expression pathways to allow bacterial survival under a multitude of unfavourable conditions and is typically activated by environmental stresses such as nutrient deprivation" [71]. In other bacteria, the stringent response is controlled by the genes *spoT* and r*elA*. The respective gene products share sequence similarity and are involved in maintenance of a global stress response regulator, guanosine tetra- and pentaphosphates [(p)ppGpp] [72].

Although both *spoT* and *relA* genes are found in many bacteria including *E. coli*, only *spoT* gene is found in *Campylobacter* and *Helicobacter*. The *spoT* gene is important for bacterial survival inside epithelial cells, and its mutation in *C. jejuni* was shown to have a pleiotropic effect [71]. A link between *spoT* expression and CFF in other bacteria has been reported. For example, ppGpp was accumulated during CF formation of *M. smegmatis* [35]. Moreover, over-expression of ppGpp via introduction of an *E. coli* copy of *relA* gene induced CF production by these bacteria [35]. In the closely related bacteria *H. pylori*, *spoT*

mutation resulted in accelerated rate of CF formation and decreased resistance to aerobic shock and acid stress [73]. A similar observation was reported for the *spoT* mutant of *C. jejuni* [71].

Factors involved in bacterial cell shape maintenance

The main structural component involved in the maintenance of a bacterial cell shape is PG. It is the major element of the cell wall in Gram-positive bacteria, whilst Gram-negative bacteria also have additional structures outside this layer that can add to strength and rigidity.

The PG of *E. coli*, in which it was studied in detail, is composed of disaccharide-pentapeptide units containing two amino sugars *N*-acetylglucosamine and *N*-acetylmuramic acid, which are connected by a β-1,4 glycosidic bond. PG in other bacteria may have some difference compared to that in *E. coli*. In particular, PG of *H. pylori* was found to have very different composition of muropeptides [74]. Because of the overall close genetic, biochemical and morphological relationship between *C. jejuni* and *H. pylori*, their PGs are likely to be more similar in structure between each other that to that of *E. coli*.

The amount of PG can be indicative of the proportion of spiral bacteria present. It was found that the yield of PG extracted from CF cells of *C. coli*, *C. jejuni* and *C. fetus* was much lower than that from RF cells. [75]. Remarkably, PG was always obtainable from *C. fetus*, coincident with inability of this subspecies to form CF. It was therefore suggested that transformation of *C. jejuni* and *C. coli* into CF may be induced by partial degradation of PG. Among a number of factors involved in the biosynthesis of PG in a model organism *E. coli* are PG hydrolases that are also required for bacterial cell division. A major class of enzymes involved in the hydrolysis of PG is *N*-acetylmuramoyl-*L*-alanine amidases. In case of *E. coli*, there are five known *N*-acetylmuramoyl-*L*-alanine amidases: AmiA, AmiB, AmiC, AmiD and AmpD [76, 77] *(Fig. 3).*

AmiA, AmiB and AmiC amidases, belonging to family 3 of amidases, have specificity for the amide bond between the sugar backbone of PG and the *L*-alanine residue of the peptide chain [77]. However, these enzymes do not hydrolyse PG units containing the anhydro-MurNAc group [78]. The enzymes of this family play an important role in the hydrolysis of PG during cell division [79]. Inactivation of genes *amiA* and *amiC* individually, but not of the *amiB* gene, inhibited cell division and resulted in the formation of long chains of cells [79].

Amidase AmpD belongs to family 2 of amidases and is specific for PG units with the anhydro-MurNAc. In contrast to other PG amidases, AmpD is found in cytoplasm, as it is necessary for PG recycling [80]. The function of an outer-membrane-located lipoprotein amidase AmiD is not fully studied [78, 81].

Owing to some overlap in their functions, some of *N*-acetylmuramoyl-*L*-alanine amidases of *E. coli* may

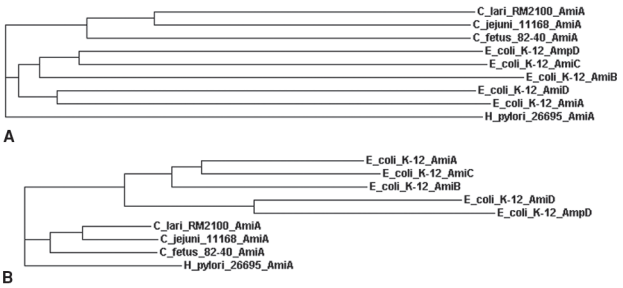

Fig. 3. Phylogenetic relationship between selected *N*-acetylmuramoyl-*L*-alanine amidases. A and B are phylograms based on the *N*- and *C*-terminal regions of the proteins, respectively. ClustalW software was used for multiples alignments and generation of phylogenetic trees. The domains were identified using Pfam database

partially substitute each other. Despite the seeming redundancy in the number of amidases in *E. coli*, each of them appears to have a specific role in bacterial lifestyle [79]. In particular, AmiC was found to be localized around the septal ring, whereas AmiA appeared to be distributed throughout the periplasm [82].

In contrast to *E. coli*, only one amidase-encoding gene is present in the genomes of *C. jejuni* and the closely related bacteria *H. pylori*. Sharing sequence similarity with other amidases found in *E. coli*, the orthologous gene products in these bacteria are annotated as AmiA, and so may be involved in PG biogenesis. As H. pylori PG undergoes substantial modifications upon bacterial entry into CF [74], it was suggested that AmiA protein may play a role in the process [83].

Indeed, the *amiA* mutation in *H. pylori* resulted in a profound effect on the bacterial ability to form spherical cells. Unexpectedly, transition to CF was characterized by the accumulation of *N*-acetyl-*D*-glucosaminyl-β(1,4)-*N*-acetylmuramyl-*L*-Ala-*D*-Glu (GM-dipeptide), which may indicate an AmiA function separate from amidase activity. Although the function of AmiA in *C. jejuni* has not been elucidated, amino acid sequence analysis also suggests a bifunctional nature of this protein. According to Pfam domain analysis, all PG amidases are characterized by high conservation in the *C*-terminal regions containing an "amidase" motif and high variability in the *N*-terminal regions. Despite close similarities in *C*-terminal domains of AmiA proteins of *C. jejuni* and *H. pylori* (indicating a common PG amidase-related function), the *N*-terminal moieties of these proteins appear to vary significantly suggesting a difference in their functions.

The discovery of the role of PG in CF formation and of some genes/products in this morphological change suggests that this is a genetically regulated process.

Although the bacterial cytoskeleton plays an important role in control of cell shape [84], some bacteria have a different shape despite similarity in their wall PG structures [85, 86]. A number of non-PG cytoskeletal components and factors involved in bacterial shape maintenance have been identified. One of them, MreB, was found to be important for cell shape maintenance [87]. The *mreB* gene

is usually found in the *dcw* (for *d*ivision/*c*ell *w*all) gene clusters involved in defining bacterial cell shape in various bacteria [88]. Remarkably, MreB contributes nearly as much to the stiffness of a cell as the PG [89–92]. MreB-like proteins are actin-related homologues required for the maintenance of bacterial cell shape by forming helical filaments underneath the cell membrane [93–95]. In *E. coli*, this protein interacts with an outer penicillin-binding protein 2 (PBP2) [96, 97]). Inactivation of *mreB* genes in *E. coli*, *Bacillus subtilis* and *Caulobacter crescentus* resulted in CF formation [90, 91, 98]. Transcriptional down-regulation of the *mreB* and *mreC* genes *Helicobacter hepaticus* also induced the formation of spherical cells [99]. It may be suggested that the *mreB*-like gene present in the genome of *C. jejuni* NCTC11168 plays a similar role in the maintenance of the bacterial cell shape. It should be mentioned that MreB is not the only known non-PG bacterial cytoskeletal element. For example, a filament-like structural protein crescentin is an essential factor required for maintaining the curved rod shape of *C. crescentus* [100].

Two other mutations, *rodA* and *pbp2*, were shown to stimulate production of spherical, osmotically resistant cells in *E. coli* [101–104]. *Pbp2* gene encodes one of the penicillin-binding proteins (*PBPs*) necessary for the maintenance and composition of the PG [96]. RodA, which is also integral for the synthesis of PG in *E. coli*, shares sequence similarity to the FtsW protein involved in the recruitment of PBP2 into the mid-cell region [105, 106].

Although *mreB*, *pbp2*, and *rodA*-like genes are present in *Campylobacter* genomes, their role in CF formation in *C. jejuni* remains to be elucidated.

Conclusion

Despite extensive studies on the molecular mechanisms and factors involved in morphological changes in other bacteria, there has been a decline in interest into the investigation of CF in both *Campylobacter* and *Helicobacter*, with most of the studies focused on other aspects of biology and epidemiology of these pathogens. This could be explained by a general consensus that in these bacteria CFs are not in a VBNC state, and so unlikely to impose any health risk. However, even considered as degenerative forms of bacteria, CF appears to play a part in a bacterial lifestyle, and so the biological role of this process deserves further investigation. In particular, preliminary data suggest a possible role of CF in biofilm formation. In addition to a possible role in the protection of a subpopulation of bacteria in a biofilm from adverse conditions, disintegration of CF cell membranes may result in leakage of genomic DNA, which is a known component of a biofilm matrix formed by *Campylobacter*. As a result of bacterial response to stress, CF formation seems to play a role in bacterial adaptation to changing environmental conditions, and may therefore be a regulated and genetically determined process, as in the case of other bacteria. Further studies focusing on deciphering the genetic and biochemical mechanisms involved in CF formation in *C. jejuni* are essential for understanding of the role of morphological changes in bacterial survival in the environment and mechanisms of transmission of this pathogen from various sources of infection. Clarification of a possible role it may play in pathogenesis and/or in resistance to stress response may ultimately assist in the development of novel antibacterial drugs.

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