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# *Campylobacter jejuni*: Components for adherence to and invasion of eukaryotic cells

## *Campylobacter jejuni: Faktoren für Adhärenz an und Invasion von Eukaryontenzellen*

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**Summary**

*Campylobacter* (*C.*) *jejuni* is the most important reported cause for bacterial diarrhoea. The infection can be accompanied by fever and abdominal cramps and in rare cases the Guillain-Barré syndrome or reactive arthritis can develop as a post-infection complication. Several biological properties of *C. jejuni*, e. g. motility and chemotaxis, contribute to the biological fitness of the pathogen. For this, deficiencies in the function of these features clearly reduce the pathogenicity of *C. jejuni* without being a virulence factor per se.
Opposing to this, there are two essential requirements to determine the virulence of *C. jejuni* which represent the adherence to, and the invasion of host cells. Thereby, adherence, as a virulence factor, is mediated by many different bacterial-derived components like proteins but also by several oligo- and polysaccharide structures that are linked to surface proteins but also to the flagella.
In addition, several invasion-relevant features of *C. jejuni* have been detected so far. Whereas some of them are described functionally to modulate cytoskeleton arrangement of the host cell, others are only described as invasion relevant. Indeed, investigations with respect to the pathogenic potential of some adherence- and invasion-relevant components did not give identical results indicating that their relevance might depend on the interplay of the respective *C. jejuni* strains used in these studies with the corresponding host cells.
This review summarizes the *C. jejuni* components for adherence to and invasion of host cells together with their particular mode of action if known.

**Keywords:** *Campylobacter jejuni*, adherence, invasion

**Zusammenfassung**

*Campylobacter* (*C.*) *jejuni* ist der wichtigste gemeldete Erreger der bakteriellen Diarrhoe. Neben den klassischen Durchfallsymptomen, einschließlich Fieber und abdominellen Krämpfen, können sich das Guillain-Barré Syndrom, aber auch reaktive Arthritis im Anschluss an das infektiöse Geschehen einstellen. Verschiedene Eigenschaften von *C. jejuni*, wie z. B. die Motilität aber auch Chemotaxis, tragen zur biologischen Fitness des Erregers entscheidend bei. Einschränkungen dieser Fähigkeiten reduzieren die Pathogenität von *C. jejuni*, ohne dabei per se als Virulenzfaktoren gelten zu können.
Im Gegensatz hierzu stehen Faktoren des Erregers, die vor allem seine Virulenz bestimmen, wie z. B. die Adhärenz an und die Invasion in Wirtszellen. Die Adhärenzeigenschaften werden von verschiedenen bakteriellen Komponenten, wie beispielsweise Proteinen, aber auch Oligo- und Polysaccharidstrukturen, welche Protein-, aber auch Flagellar-gebunden sind, bestimmt. Zusätzlich sind verschiedene invasionsrelevante Komponenten von *C. jejuni* bekannt. Während von einigen dieser Invasionsfaktoren gezeigt werden konnte, dass sie die Zytoskelettstruktur der Wirtszelle verändern, sind andere lediglich als invasionsrelevant beschrieben. Allerdings sind die Forschungsergebnisse im Hinblick auf die Bedeu-

tung einiger Adhärenz- aber auch Invasionsfaktoren nicht einheitlich, was darauf hinweisen könnte, dass die Funktion dieser Faktoren an den jeweiligen *C. jejuni*-Stamm und die eingesetzte Wirtszelllinie gebunden ist.
Diese Übersichtsarbeit fasst die Faktoren von *C. jejuni* zusammen, welche die Adhärenz an und die Invasion in Wirtszellen vermitteln. Der jeweilige Wirkungsmechanismus der relevanten Proteine wird, soweit bekannt, beschrieben.

**Schlüsselwörter:** *Campylobacter jejuni*, Adhärenz, Invasion

## Introduction

*Campylobacter* (*C.*) *jejuni*, a spiral shaped, Gram-negative, microaerophilic bacterium, belongs to the delta epsilon group of proteobacteria. *C. jejuni* is flagellated leading to a corkscrew motility but does not possess the capability to form spores.

The first complete genome sequence of a *C. jejuni* strain (NCTC11168) was published in the year 2000. The circular genome has a size of 1.6 Mbp encoding 1,654 proteins and 54 stable RNA species (Parkhill et al., 2000). Meanwhile the complete genome sequences of 14 strains are available at the NCBI genome database. Compared to other intestinal pathogens like *Salmonella* spp., *C. jejuni* has a comparatively small genome and a rather low G+C content of approximately 30% (Gaskin et al., 2009). Plasmids encoding for antibiotic resistance or a type-IV-secretion system are described in several, but not all strains sequenced so far (Bacon et al., 2000; Batchelor et al., 2004; Louwen et al., 2006).

Unlike e. g. *Escherichia* (*E.*) *coli*, *C. jejuni* is incapable to ferment glucose due to the lack of the glycolytic enzyme phosphofructokinase. Only a livestock-adapted subgroup of *C. jejuni* strains is able to utilize L-fucose (Muraoka and Zhang, 2011; Zautner et al., 2012 a). Instead, *C. jejuni* is able to metabolize free amino and keto acids which have been generated by accompanying bacterial species in its ecological niche or directly from the respective host (Lee and Newell, 2006). Due to the expression of a periplasmic γ-glutamyl-transpeptidase and a periplasmic asparaginase, a non-livestock adapted group of *C. jejuni* strains which is unable for L-fucose utilization exhibits an extended amino acid metabolism (Hofreuter et al., 2008; Zautner et al., 2011). In comparison, the respiratory chain of *C. jejuni* is distinctly complex. For instance, succinate, formate, malate, D-lactate as well as hydrogen or NAD(P)H can serve as electron donors. In addition, even anorganic chemical substances such as sulfite can be utilized as a respiratory electron donor, giving *C. jejuni* also a chemolithotrophic-like character (Hoffman and Goodman, 1982; Kelly, 2001; Sellars et al., 2002; Velayudhan and Kelly, 2002; Myers and Kelly, 2005).

*Campylobacter* spp. are generally common in intestinal inhabitants of several animal species including mammals and birds where they colonize various mucosal surfaces (Gilbreath et al., 2011). In particular, the microaerophilic conditions in poultry combined with a blood temperature around 41°C favour their colonization by *C. jejuni*. Consequently, the consumption of contaminated chicken meat is one of the major sources of *C. jejuni* infections in humans. In addition, consumption of beef or raw milk contributes significantly to campylobacteriosis in humans, whereas the direct contact between individuals has no relevance (Dasti et al., 2010). In accordance with the pervasive presence of the pathogen in poultry, infections with *C. jejuni* meanwhile represent the most important bacterial caused food-borne diseases with 60 000 reported cases in Germany and 2,5 million cases in the USA, annually (Dasti et al., 2010; Friedman et al., 2000). Once *C. jejuni* has entered the intestine it has to overcome the intestinal microbiota barrier located on and within the intestinal mucin layer (Masanta et al., 2013). After that the epithelium is colonized. This is often accompanied by symptoms of acute diarrhea which can vary from mild watery to bloody and might include fever and abdominal cramps. Thereby, the level of invasiveness varies and depends on the respective *C. jejuni* strain (Black et al., 1988; van Vliet and Ketley, 2001). In addition, the Guillain-Barré syndrome or reactive arthritis can follow the acute phase of the infection (Hannu et al., 2002; Hughes and Cornblath, 2005; Zautner et al., 2014).

This article will summarize bacterial components that mediate two important features in the interplay between *C. jejuni* and its, first of all, human host: adherence and cellular invasion.

## Diminished pathogenicity by decreased biological fitness

The pathogenicity of *C. jejuni* depends on its capability to interact and, subsequently, invade the respective host cell. Furthermore, other factors are essential to evolve the pathogenic potential, which are not virulence factors per se, but constitute a vital requirement for infection. In this context, most notably, flagellar motility and chemotaxis have to be mentioned. *C. jejuni* is adapted to reside within a viscous mucus layer which covers the gastric epithelial cells. This has led to the development of a powerful flagellar apparatus that confers motility to the bacterium and enables it to move with high velocities inside its particular microenviroment and to reach potential target cells. Consequently, motility of *C. jejuni* was shown to be a key factor for intestinal colonization and *C. jejuni* mutants with motility defects lost their competence to infect host cells (Morooka et al., 1985; Yao et al., 1994; Wassenaar and Blaser, 1999).

The chemoreceptors of *C. jejuni*, which detect variations of chemotaxin concentrations surrounding the bacterium, depict a direct control for the activity of the flagellar apparatus. Altogether ten different chemoreceptors and two aerotaxis genes have been described so far, whereby only three of the chemoreceptors have been characterized with respect to their chemoattractants or chemorepellents (Hartley-Tassell et al., 2010; Tareen et al., 2010; Rahman et al., 2014). These chemoreceptors are either membranous or located in the cytoplasm and interact with a kinase, a response regulator and a coupling protein, respectively. A chemoattractant bind-

ing to the chemoreceptor reduces the amount of phosphorylated response regulator, which finally diminishes its interaction with the flagellar apparatus. The lack of response regulator-flagellar switch interaction causes a counterclockwise flagellar rotation leading to bacterial swimming. Otherwise, the absence of a chemoattractant promotes phosphorylation of the response regulator and binding to the flagellar switch. Consequently, the flagellum turns clockwise which is accompanied by tumbling and direction changes (Marchant et al., 2002; Zautner et al., 2012b; Lertsethtakarn et al., 2011). Due to the fact that the chemotactical system of *C. jejuni* directly governs the motility of the pathogen, mutations of chemoreceptors or accessory proteins strongly decreases the motility of *C. jejuni* and, thus, pathogenicity (Golden and Acheson; 2002; Hendrixson et al., 2001; Tareen et al., 2010; Bereswill et al., 2011).

## Adherence-mediating molecules of *C. jejuni*

The adherence of *C. jejuni* to the epithelial cells of the intestine is an essential requirement prior to the process to invasion. During the last two decades several proteins, but also carbohydrates have been characterized that contribute significantly to the adherence of *C. jejuni* both, in vitro and in vivo.

One of the first *C. jejuni* proteins described to be involved in bacterial adhesion is Peb1A which represents the periplasmic binding protein component of an aspartate/glutamate ABC transporter. In addition this protein could be shown to mediate adherence to HeLa cells and to be important for the colonization of mice and, therefore, is believed to possess a dual function (Pei and Blaser, 1993; Pei et al., 1998; Leon-Kempis et al., 2006; Müller et al., 2007). However, the generation of a corresponding knockout mutant in the same *C. jejuni* strain (81-176) by another group revealed no differences in cellular adhesion. This discrepancy might be explained by the utilization of different cell lines or the conditions of their respective bacterial invasion assays (Novik et al., 2010). The *C. jejuni N*-glycosylated protein Peb3 has also been shown to serve as an adhesion protein but is also suggested to be a transport protein which might be involved in utilization of 3-phosphoglycerate (Min et al., 2009). Furthermore, JlpA, a *N*-linked glycosylated lipoprotein of *C. jejuni* which is exposed to the surface of the bacterium, mediates adhesion to Hep-2 cells via heat shock protein (Hsp) 90α. This particular interaction activates signalling pathways leading to NFκB and p38 MAP kinase activaton which indicates an involvement in the inflammatory host cell response following *C. jejuni* infection. Indeed, the results of another group investigating the role of JlpA in cellular adherence of *C. jejuni* are not consistent. Knockout mutants of *jlpA* gave different results regarding their potential to adhere to host cells. The reasons for this might be the same as in the case of Peb1A mentioned above (Jin et al., 2001, 2003; Scott et al., 2009; Novik et al., 2010). CapA represents a surface-localized lipoprotein of *C. jejuni*, which mediates adherence to Caco-2 cells and plays an important role in the colonization of the chicken gut (Ashgar et al., 2007). Another protein, Cj0091 is important for the adherence of *C. jejuni* to INT407 cells (later identified as HeLa contaminated cell line) and also contributes to the colonization of chicken (Oakland et al., 2011). In addition, Cj0268c enhances the adherence to Caco2 cells although this protein seems to be localized in the periplasmic space with no access of its C-terminus to the bacterial surface and a directed mutagenesis of gene *cj0497* indicated this gene to encode for a potential adhesion protein (Javed et al., 2010; Tareen et al., 2013). However, for Cj0268c an involvement in *C. jejuni* induced immunopathogenesis was demonstrated in vivo (Heimesaat et al., 2014). The flagellar apparatus of *C. jejuni* has been shown to secret proteins into the extracellular milieu. One of these proteins is FlaC, which is homologous to the *N*- and *C*-termini of flagellin A and B, respectively, but without the central part of these proteins. FlaC has been demonstrated to bind to Hep-2 cells and, for this, can be judged as an adhesin since FlaC mutants have a strongly reduced capacity to invade host cells (Song et al., 2004). Homologs of the CJIE1 prophage are detected in a significant percentage of *C. jejuni* isolates. While the patient symptoms were not affected by the presence or absence of this prophage, cell culture assays indicated an increased adherence in *C. jejuni* strains carrying CJIE1 (Clark et al., 2012). A functional type VI secretion (T6SS) system was recently identified in a chosen number of *C. jejuni* isolates. This system has been shown to play an important role for the adherence of the pathogen to human T84 colon epithelial cells as well as to murine RAW 265.7 macrophages since non-random knockout mutants of the T6SS genes *hcp1* and *icmF1* resulted in a clearly adherence-reduced phenotype relative to the parental strain (Lertpiriyapong et al, 2012). A minority of *C. jejuni* strains carries a plasmid termed pVir. This plasmid encodes genes which are involved in DNA uptake or the transport of proteins by a putative type IV secretion system. Mutations of two of the plasmid encoded genes, *comB3* and *virB11*, reduced the adherence to INT407 cells significantly (Bacon et al., 2000).

Some adhesion proteins of *C. jejuni* have been shown to interact with the extracellular matrix component fibronectin which, on his part, binds to membrane spanning integrins. Major outer membrane protein MOMP of *C. jejuni*, for example, is able to bind to fibronectin, but also to the membrane of INT407 cells (Moser et al., 1997). Recently, it could be shown that MOMP is *O*-glycosylated, which significantly affects the conformation of the molecule. For this, *O*-glycosylation maintains the three-dimensional structure of MOMP which allows binding to histo-blood group antigens (BsAgs) but also promotes adhesion to host cells (Mahdavi et al., 2014). In addition, CadF, another outer membrane protein, has been shown not only to interact with fibronectin. It possesses bifunctional qualities as it facilitates a time-dependent activation of the small Rho family GTPases Rac1 and Cdc42 (Konkel et al., 1997; Krause-Gruszczynska et al., 2007). Furthermore, also FlpA has the property to mediate the attachment of the pathogen to epithelial cells by fibronectin binding and plays an important role for the colonization of chicken (Flanagan et al., 2009; Konkel et al., 2010). Thereby it is possible that the binding of the *C. jejuni* adhesins CadF and FlpA to fibronectin promote the activation of the $\alpha_5ß_1$-integrin receptor as an initial step for bacterial invasion (Eucker and Konkel, 2012).

Adhesion proteins that directly interact with epithelial cells mediate host cell adherence by *C. jejuni*. To facilitate this particular function, the correct folding of these pro-

teins and their export to the outer membrane has to be ensured. The periplasmic protein HtrA which possesses chaperone and protease activity has been shown to be required for efficient adherence since especially the loss of its chaperone function reduces host cell binding (Bæk et al., 2011). Furthermore, a functional deletion of protein Peb4 reduced the adherence of *C. jejuni* strain NCTC 11168 to INT407 cells to 1–2% (Asakura et al., 2007). Meanwhile, the crystal structure of this protein has been published supporting the idea that Peb4 is a chaperone with respective function in protein export. For this, the lack of delivered adherence-mediating surface proteins, as in case of the *htrA* mutant, might be responsible for its adhesion-relevant phenotype (Kale et al., 2011).

In addition to the proteins mentioned above, saccharide structures are described to be important for the bacterial adhesion to host cells, not only to stabilize a particular three-dimensional structure as in case of MOMP (described above), but for the direct interaction of *C. jejuni* with host cells. Altogether 19 classes of genetic loci for the synthesis of lipooligosaccarides (LOS) in *C. jejuni* are known to date. Thereby, the genes responsible for the generation of LOS in strain 81116 are termed *wlaRG*, *wlaTB* and *wlaTC* and it could be shown that mutants of all three genes revealed a decreased adherence to chicken embryo fibroblasts (Holden et al., 2012). The relevance of LOS structures for invasion has been published several times. However, most of these papers did not investigate altered adherence in particular, even diminished adherence might be the actual reason for the loss of infectivity towards host cells (Bacon et al., 2001; Kanipes et al., 2004; Bachtiar et al., 2007; Louwen et al., 2008).

*C. jejuni*, together with *Haemophilus influenzae*, is equipped with an *N*-linked protein glycosylation system. Even though the biological function of *N*-linked glycosylation in *C. jejuni* is not clear yet, knockout mutations in the corresponding gene cluster showed reduced adherence to host cells and, consequently, diminished invasion (Szymanski et al., 2002; Karlyshev et al., 2004).

The flagellins of *C. jejuni* are *O*-linked glycosylated by pseudaminic acid (PseAc) and legionaminic acid (LegAm). Glycosylation with PseAc or derivates of PseAc is a prerequisite for the assembly of an intact and functional flagella filament (Thibault et al., 2001; Logan et al., 2002). Thereby, the genome organization of the locus for the synthesis of PseAc in different strains is not unique. However, a mutation in the gene *pseA* in *C. jejuni* strain 81-176 leads to the loss of the acetamidino form of PseAc which is accompanied by a moderate reduction of adherence and subsequent invasion of INT407 cells (Guerry et al., 2006). Another flagellar modification in *Campylobacter* is the glycosylation by legionaminic acid (LegAm) (McNally et al., 2007). Although LegAm is present on the surface of the bacterial flagellum there is no direct evidence for the contribution of LegAm with respect to host cell adherence. Only one publication exists, where a sulphite: cytochrome c oxidoreductase-deficient mutant which exhibits reduced adherence to Caco-2 cells also downregulates the transcription of genes responsible for the synthesis of LegAm. However, a direct link between both incidents is not shown (Tareen et al., 2011).

While the relevance of PseAm and LegAm for the bacterial attachment to host cells is difficult to assess, the capsule polysaccharides (cps) have obviously been shown to be an essential factor for *C. jejuni* virulence including adherence, since a functional knockout of the *kpsE* gene encoding a transporter for cps almost eliminates the attachment of the mutant strain to INT-407 cells (Bacon et al., 2001; Bachtiar et al., 2007). Furthermore, *C. jejuni* cocultured with epithelial cells downregulates the transcription of genes for the synthesis of cps significantly, which leads to a clearly diminished adherence to HCT-8 epithelial cells (Corcionivoschi et al., 2009). The adherence capacity of cps was also demonstrated as a non-capsulated mutant of *C. jejuni* strain 81-176 showed an almost 10-fold decrease in adherence compared to the wild-type strain (van Alphen et al., 2014).

## *C. jejuni* components for cellular invasion

The invasion of intestinal cells by *C. jejuni* is believed to be the most important reason for colon damage and accompanying diarrheal disease. Infant monkeys infected with *C. jejuni* developed diarrhea whereby intracellular bacteria were detected in membrane bound vacuoles and free in the cytoplasm. In addition, damaged epithelial cells could be localized in the lumen of the colon (Russel et al., 1993). The outcome of experiments to investigate the *C. jejuni* invasion of host cells is not unique, but differs regarding the contribution of components that constitute the host cell cytoskeleton. *C. jejuni* invasion of INT407 cells could be blocked by the depolymerization of microtubules but not microfilaments. This observation was supported by another study, which detected a colocalization of *C. jejuni* not only with microtubules but also with motor protein dynein (Oelschlaeger et al., 1993; Hu and Kopecko, 1999). In contrast, during the invasion of Hep-2 cells, *C. jejuni* attachment could be seen in areas with an intracellular network of actin-like filaments indicating microfilament involvement. Furthermore, microfilament depolymerizing chemicals could significantly reduce invasion of INT407 cells (De Melo et al., 1989; Monteville et al., 2003). Taken together, the exact mode of cellular invasion by *C. jejuni* might depend and vary on the interplay between particular bacterial strains with their particular host cells.

Many proteins, but also carbohydrate components have been associated to the process of invasion. However, it cannot be excluded that in case of carbohydrate structures like sialylated lipooligosaccharides or capsular polysaccharides at the bacterial surface, their particular contribution to cellular invasion might be due to adherence rather than to entry of *C. jejuni* into the host cell (Bacon et al., 2001; Kanipes et al., 2004; Bachtiar et al., 2007; Louwen et al., 2008).

In contrast to other enteropathogenic bacteria like *Yersinia enterocolitica* or *E. coli*, *C. jejuni* is not equipped with a type-III-secretion system for direct injection of effector proteins into the host cell. Instead, *C. jejuni* secretes proteins via a type-III-homologue secretion system in its flagellar apparatus into the surrounding environment. These proteins are designated as *Campylobacter* invasion antigens (Cia) which are required for the invasion of and intracellular survival in host cells (Konkel et al., 1999). CiaB, localized in the cytoplasm of the host cell, was reported to be important for the process of

invasion but not for adherence of *C. jejuni*. Furthermore, CiaB seems to be involved in bacterial protein secretion itself since a *ciaB* knockout mutant has lost the ability to release eight proteins into the culture medium. Unfortunately, the invasion-relevant phenotype of CiaB could not be confirmed by Novik et al. (2010), where the *ciaB*-deficient mutant did not show altered invasion compared to the wildtype. The differences in the results of the respective groups might eventually be explained by the usage of different cell lines to determine bacterial invasion. Furthermore, since the invasion-deficient mutant with the strongly reduced invasion capacity was not functionally complemented, an alteration within the genome incoherent of the site directed mutation might be responsible for their lack of infectivity (Konkel et al., 1999; Novik et al., 2010). CiaC is another flagella-secreted protein which has been investigated regarding its function as a virulence factor of *C. jejuni*. This protein is translocated into host cells following bacteria-host cell association. Thereby, similar to CiaB, this protein is important for cellular invasion but not adherence. It exhibits a restricted secretion profile with the lack of one protein in a *ciaC* mutant. Furthermore CiaC is partially responsible for the recruitment of Rac1 at cellular sites associated with *C. jejuni* which, in turn, mediates rearrangements of the host cell cytoskeleton and membrane ruffling (Christensen et al., 2009; Neal-McKinney and Konkel, 2012; Eucker and Konkel, 2012). Recently, CiaD has been investigated regarding its particular contribution on cellular invasion by *C. jejuni*. Thereby, it was found that CiaD is involved in Erk1/2 and p38 activation which promotes the release of interleukin-8. Furthermore the CiaD-supported activation of MAP kinase Erk1/2 facilitates the invasion by *C. jejuni* by phosphorylation of cortactin, known to promote polymerization and rearrangement of the cytoskeleton (Konkel et al., 2013; Samuelson and Konkel, 2013). Finally the protein CiaI was demonstrated to enable the intracellular survival of *C. jejuni* in so called *Campylobacter*-containing vacuoles (CCV; Buelow et al., 2011).

The results regarding the invasion capacity of protein Cj0997 are incoherent. In a first publication, a *cj0997* mutant was described to be invasion deficient, but to be fully motile. A later study confirmed the strongly reduced capacity of the mutant to invade host cells, but, in contrast to the first publication, the mutant exhibited reduced motility. This would indicate that the reduced invasiveness is due to its diminished motility, which might be correlated with the absence of this protein in an unknown fashion (Goon et al., 2006; Novik et al., 2010). Like gene *cj0997*, several other genes are under σ28 control, which governs the transcription of *flaA* but also other genes for the constitution of the flagellar apparatus. These genes have been designated as flagellar coexpressed determinants (feds). Investigations of the corresponding mutants detected a colonization-reduced phenotype in mice for several fed genes, but only *fedA* was shown to be important for the invasion of host cells (Barrero-Tobon and Hendrixson, 2012). The cytolethal distending toxin (CDT) has been shown to mediate cell cycle arrest (Lara-Tejero and Galan, 2000). The role of *C. jejuni* CDT for the process of invasion seems to depend on the origin of the respective host cell line. While CDT mutants were clearly reduced in their potential to invade human HeLa cells, no difference between wildtype strain and mutant was observed applying avian macrophage HD-11 cells (Biswas et al., 2006; Jain et al., 2008). Another *C. jejuni* protein that was shown to be important for cellular invasion is Cj1496c. Comparison of an insertion mutant as well as an in-frame deletion mutant with the wildtype strain, revealed both mutants to be defective for the invasion of INT-407 cells (Kakuda and DiRita, 2006). The recently described type VI secretion system was also shown to be relevant for invasion. However as mentioned above, mutations of the T6SS exhibited an adherence-reduced phenotype which might be the actual reason for reduced invasion. This might also be the case regarding the invasion capacity of prophage homolog CJIE1 (Clark et al., 2012; Lertpiriyapong et al, 2012).

Due to the detection and characterization of all these components that participate in the invasion of host cells by *C. jejuni*, our knowledge how this important pathogen facilitates cellular uptake has grown. However, further genes have been detected that contribute to the invasion process (Novik et al., 2010). But even these virulence factors together with the ones already characterized may not represent the complete picture yet.

## Conflict of interest

The authors declare that no competing interests exist.

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