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Review Article

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Review on Some Virulence Factors Associated with *Campylobacter* Colonization and Infection in Poultry and Human

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Introduction

Campylobacter is one of the most important four global diarrheal diseases. It is considered to be the most common bacterial cause of human gastroenteritis in the world causing a disease called campylobacteriosis. In developing countries, *campylobacteriosis* in children under the age of 2 years are especially frequent and sometimes resulting in death [1]. Mainly *C. jejuni* and *C. Coli* are well recognized causes of human campylobacteriososis with symptoms ranging from mild watery diarrhea to serious neuropathies [2]. Poultry (particularly chicken and contaminated raw chicken carcasses) is considered to be the main source for human campylobacteriososis. Other sources such as water, raw milk, Cattle, sheep, pigs, cats, dogs, vehicles, rodents and insects are known as possible sources for not only human but also poultry campylobacteriosis. After being colonized by Campylobacter spp. Chicken in contrast to human, do scarcely develop pathological lesions [3]. The high body temperature of Poultry species provides an optimal environment for the growth of thermophilic Campylobacter species particularly C. jejuni and C. coli which make poultry constitute the main source of human campylobacteriosis [4].

Campylobacter spp. are Gram negative rods, 0.5 - 8µm long and 0.2 - 0.5µm wide with characteristically curved, spiral, or S-shaped cells; coccal forms may be seen under sub-optimal conditions. They generally have a single polar unsheathed flagellum at one or both ends. The motility of the bacteria is characteristically rapid and darting in corkscrew fashion, a feature by which their presence among other bacteria can be detected by phase-contrast microscopy [5,6].

On Skirrow or other blood-containing agars, characteristic *Campylobacter* colonies are slightly pink, round, convex, smooth and shiny, with a regular edge. On charcoal-based media such as mCCDA, the characteristic colonies are greyish, flat and moistened, with a tendency to spread, and may have a metallic sheen. *Campylobacter* spp. require microaerobic conditions consisting of (5% O2, 10% CO2 and 85% N2) [7]. They neither ferment nor oxidase carbohydrates. Energy is obtained from amino acids or tricarboxylic acid cycle intermediates, not carbohydrates. Some species, particularly C. *jejuni, C. coli and C. lari,* are thermophilic, grow optimally at 42°C [8].

Despite over 30 years of research, *Campylobacteriosis* is the most prevalent bacterial cause of foodborne infection in many countries including in the EU and the USA [9]. As mentioned before that poultry species are important reservoirs for the transmission of *Campylobacter* species and their high body temperature provides an optimal environment for the growth of the organism [4]. It is important to explore further the relationships between certain *Campylobacter* virulence genes and their capacity for survival in poultry meat, and hence their contribution to the incidence of *Campylobacteriosis* [10] and the large genetic diversity of *Campylobacter* must be considered in epidemiological evaluations and microbial risk assessments of *Campylobacter* in poultry [11,12].

As a first step, colonization of the intestine requires the ability to move into the mucus layer covering the intestinal cells. *Campylobacter* motility is conferred by the polar flagella, which together with their 'cork-screw' shape allow them to efficiently penetrate this mucus barrier [13,14]. The most important virulence factor that has been studied and well characterized in *Campylobacter* spp. was the flagellin, which is encoded by the *flaA* gene [15]. The global regulator, *CsrA* (Carbon starvation regulator) gene, has been well characterized in several bacterial genera and is known to regulate a number of independent pathways via a post transcriptional mechanism, but remains relatively uncharacterized in the genus *Campylobacter* [16].

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Many of virulence genetic factors connected with Campylobacter invasiveness are placed on the pVir plasmid for example, *virB11* gene that encodes the IV secretory system protein. It has been showed that strains with mutation in the *virB11* sequence have much lower adhesion and penetration ability in vitro in comparison to original strains, as well as lower pathogenicity 0069n vivo the plasmid gene *virB11* [17]. One of the most important genes responsible for *Campylobacter* invasion is the *CiaB* (*Campylobacter* invasive antigen B) gene which is known to be involved in the translocation of *Campylobacter* into host cells for the purpose of host cell invasion and also plays a significant role in cecal colonization in chicken [18]. The invasion-associated marker (*iam*) gene is one of most important factors responsible for *Campylobacter* invasion of host cell and this gene was first reported [19] and was detected in 85% of invasive strains and 20% of non-invasive strains. The *pldA* gene is also related to cell invasion and is responsible for the synthesis of an outer membrane phospholipase that is important for cecal colonization [18,20]. That gene encodes proteins associated with increased bacterial invasion on cultured epithelial cells [21]. Cytolethal distending toxin (CDT) in which *CdtB* subunit is the active toxic unit. *CdtA* and *CdtC* required for CDT binding to target cells and for the delivery of *CdtB* into the cell interior [22]. The toxin is retrograde transported into the nuclear compartment, where the *CdtB* subunit exhibits type I DNase activity. Cellular intoxication induces DNA damage and activation of the DNA damage response, which results in arrest of the target cells in the G1 and/or G2 phases of the cell cycle and activation of DNA repair mechanisms, cellular distention and nuclear enlargement, and Cdc2 and ataxia-telangiectasia-mutated protein (ATM) phosphorylation. Cells that fail to repair the damage will senesce or undergo apoptosis [23]. Considering the important role that toxins have in the pathogenesis of *Campylobacteriosis* and other infections, all knowledge generated in this area will serve to propose and develop new strategies for the control of pathogens [24]. The thermal stress response of bacteria is mostly carried out by the induction of the expression of heat shock proteins (HSPs). These HSPs have an important function in thermotolerance as well as in the response to other stresses by acting as chaperones to promote the folding of most cellular proteins and proteolysis of potentially deleterious, misfolded proteins. Several HSPs have been identified in *C. jejuni*, including the *GroESL, DnaJ, DnaK* and *ClpB* proteins [25-28]. However, a role in *C. jejuni* pathogenesis has only been demonstrated for the *DnaJ* protein, as a *C. jejuni dnaJ* mutant was unable to colonize chickens [25]. The importance of the C. *jejuni* thermal stress response is also indicated by the link between thermoregulation and chicken colonization through the *racR* regulatory protein [29] Cited by [30]. *dnaJ* was detected in 100% of all chicken fecal samples examined while there is a difference in human samples with detection rate of 98% [31]. Relatively similar results were obtained in Egypt by [32] who confirmed these results with gene expression of *dnaJ* and using 23srRNA as a housekeeping gene. On the other hand our results in human samples agreed with [20] who detected *dnaJ* gene in 46% and 50% of human *C. jejuni* and *C. coli* samples respectively although there are some differences in results of *dnaJ* from chicken samples which came in a rate of 69% and 70% for C. *jejuni* and C. coli respectively [33], detected *dnaJ* gene in 100% of Human *C. jejuni* and *C. coli*. High detection of *dnaJ* gene in chicken than human host that reported by many authors confirmed the data that revealed importance of *dnaJ* gene in broiler cecal colonization by [34]. Two-component regulatory system, *RacR-RacS* (reduced ability to colonize) system, that is involved in a temperature-dependent signalling pathway was identified [29]. A mutation of the response regulator gene *racR* reduced the organism's ability to colonize the chicken intestinal tract and resulted in temperature-dependent changes in its protein profile and growth characteristics. Authors added that C. *jejuni dnaJ* gene is adjacent to and under the transcriptional control of *racR*. [31] detected *racR* gene in 98.2 and 100% of C. *jejuni* isolates from human and broiler respectively [35], reported partially similar results in *C. jejuni* but not *C. coli*. They detected *racR* gene in 84.9% and 95.6% of *C. jejuni* from human and poultry respectively [36], detected *racR* gene in 100% of *C. jejuni* isolated from Human diarrheal patients in Bangladesh [37], reported *racR* gene in 98.3 % of *C. jejuni* isolates from children's ≤14 years who were treated for diarrhoea at emergency rooms in north-eastern Brazil [38], detected *racR* gene in 95% and 0% of human *C. jejuni* and *C. coli* respectively. And in 76% and 79% of chicken *C. jejuni* and *C. coli* respectively. Similar results revealed by [32] in Egypt.

Infection with *C. jejuni* usually causes uncomplicated gastroenteritis; however, in rare cases can lead to the Guillain-Barré syndrome (GBS), a post infectious immune-mediated disorder of the peripheral nerves and nerve roots [39]. The global incidence of GBS ranges from 0.4 to 4.0 (median 1.3) cases per 100,000 people annually, occurring slightly more often in adolescents and young adults [40]. Results of [41] review analysis suggest that 31% of 2,502 GBS cases included in this review are attributable to Campylobacter infection. Molecular mimicry between lip oligosaccharides (LOS) present on the cell wall of *C. jejuni* and gangliosides found in the human nervous system is thought to play a critical role in the pathogenesis of *C. jejuni*-related GBS [42]. The wlaN, *cgtB* and *waaC* are LOS (lipo-oligosaccharides) associated genes while wlaN and *cgtB* are involved in β-1,3 galactosyltransferase production. These two genes are associated with *waaC* gene which encodes heptosyltransferase I [43]. The *waaC* gene, which encodes heptosyltransferase I, is responsible for transferring the first l-*glycerod- manno*-heptose residue to the inner core of LOS [44]. The wlaN gene, which encodes a beta-1,3 galactosyltransferase, is responsible for biosynthesis GM1-like structure whereas *cgtB* (which encodes another beta-1,3 galactosyltransferase) catalyzes the biosynthesis of the carbohydrate moieties analogous to GM2 [45]. Sialyltransferase encoded by the *cst*-II gene in *C. jejuni* is associated with risk of developing GBS [46]. On the other hand, the *cst*-II gene has been linked to the invasiveness of *C. jejuni* for intestinal epithelial cells [47]. *C. jejuni* gene ggt encoding the periplasmic gamma-glutamyl transpeptidase (GGT) seems to play a pivotal role in the enteric colonization. GGT has been shown in chicken model to be important in long lasting gut colonization, and in vitro it has been shown that GGT plays a significant role in *C. jejuni*-mediated apoptosis [48,49] detected *cst-II* and *ggt* genes in 83.6% and 32.7% of 55 examined *Campylobacter jejuni* human origin isolates and 40% and 5.5% of

55 *Campylobacter jejuni* broiler meat origin isolates in Chile [50], detected *cgtB, wlaN* and *waaC* genes in 7.69%, 30.77% and 57.69% of isolates respectively in Bangladesh [51], detected *wlaN* and *cgtB* in 20% and 6.7% of 30 *C. jejuni* isolates from Patients with Diarrhea in Rosario, Argentina.

Conclusion

Campylobacter epidemiology results should be liked with its virulence gene characterization. Although the molecular basis of pathogenicity of *Campylobacter* has not been fully elucidated, several virulence factors have been identified based on *in vitro* and *in vivo* studies. For example, *flaA, cadF, CsrA* for adhesion. *iam, virB11*, *ciaB* and *pldA* (invasion). CDT (*CdtA, CdtB* and *CdtC*) (cytotoxicity). *dnaJ* (heat shock protein). *racR* (reduced ability to colonize). *cgtB*, *waaC*, *cst*II, wlaN & ggt (ganglioside mimicry)..

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