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 campylobacteriosis 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 campylobacteriosis. 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 ‘corkscrew’ 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].
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]. Cytotoxic 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 CdtBs 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 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 CipB 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]. Similarly relative results were obtained in Egypt by [32] who confirmed these results with gene expression of dnaJ and using 23sRNA 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-glycerol- 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 (GRT) 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
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, cstl, wlaN & ggt (ganglioside mimicry).

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