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Review

Campylobacter virulence and survival factors

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ABSTRACT

Despite over 30 years of research, campylobacteriosis is the most prevalent foodborne bacterial infection in many countries including in the European Union and the United States of America. However, relatively little is known about the virulence factors in *Campylobacter* or how an apparently fragile organism can survive in the food chain, often with enhanced pathogenicity. This review collates information on the virulence and survival determinants including motility, chemotaxis, adhesion, invasion, multidrug resistance, bile resistance and stress response factors. It discusses their function in transition through the food processing environment and human infection. In doing so it provides a fundamental understanding of *Campylobacter*, critical for improved diagnosis, surveillance and control.

1. Introduction

Campylobacter are gram negative, slender, spirally curved (0.2–0.8 μm × 0.5–5 μm), microaerophilic bacteria that live as commensal organisms in the gastrointestinal tract of many domestic and wild birds and mammals. Although Fernández et al. (2008) suggested that the *Campylobacter* genus comprises 20 species and subspecies, other authors have suggested that there are 16 species with an additional 6 subspecies (On, 2001; Foster et al., 2004). With the exception of *Campylobacter gracilis* (which is non-motile) and *Campylobacter showae* (multiple flagella), all other *Campylobacter* species have a single polar unsheathed flagellum at one or both ends of the cell.

Campylobacter are of particular research interest as they consistently cause the greatest number of confirmed foodborne bacterial infections in developed countries. Thus, each year approximately 1% of Europeans suffer campylobacteriosis (Humphrey et al., 2007), costing approximately €2.4bn (EFSA, 2012). The corresponding figure for the USA is $2.9bn (Batz et al., 2011). The majority (over 90%) of these cases are caused by *Campylobacter jejuni* and to a lesser extent *Campylobacter coli*.

Poultry are the natural host for *Campylobacter* species and broilers are often colonised, especially with *C. jejuni* (EFSA, 2010a). The poultry reservoir is responsible for an estimated 80% of human campylobacteriosis cases (EFSA, 2010b). Transmission to humans is most often associated with the handling and consumption of poultry, contaminated during slaughter and carcass processing (Humphrey et al., 2007). Despite over 30 years of research, *Campylobacter* control on broiler farms remains elusive. Current approaches rely heavily on biosecurity, which is often ineffective with the majority of broiler flocks being infected by the third or fourth week of rearing (Patriarchi et al., 2009).

In the birds, *C. jejuni* establishes a colonising population in the cecal mucosal crypts, the primary site of infection, within 24 h (Coward et al., 2008). Although *Campylobacter* numbers of up to 10^8 cfu/g may be obtained, colonisation does not cause illness in the birds nor changes in the cecal mucosa (Meade et al., 2009). The gastrointestinal tract (GIT) of poultry is a hostile environment and the persistent of *C. jejuni* suggests that these bacteria are capable of adaptive responses to different environmental stresses. However, unlike other bacteria such as *Salmonella* and *Escherichia coli*, much less is known about the survival mechanisms in *Campylobacter*.

The route from environmental contaminant to chicken ceca, poultry carcass contaminant and finally human disease agent contains many hurdles but the mechanisms of survival and infection in *Campylobacter* are poorly understood. After ingestion by humans, *C. jejuni* colonises the lower gastrointestional tract (ileum, jejunum and colon) sometimes without symptoms. The outcome of disease is dependent on the immune status of the host and the virulence characteristics of the *Campylobacter* strain. In most symptomatic cases, campylobacteriosis is manifest as mild and self-limiting gastroenteritis characterised by 1–3 days of fever, vomiting and headaches followed by 3–7 days of abdominal pain with

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watery or bloody diarrhoea. However, in a minority of individuals *Campylobacter* infection is a precursor of more serious illness, including immunoreactive complications such as Guillian–Barré Syndrome (GBS) and Miller–Fisher Syndrome (MFS), a chronic and potentially fatal form of paralysis (EFSA, 2011). Greater knowledge of *Campylobacter* virulence and stress response mechanisms would facilitate new thinking and the development of innovative control technologies. The objective of this paper is therefore to summarise the current state-of-knowledge.

2. Virulence and survival factors

The genes involved in *Campylobacter* virulence and/or survival, their products and functions are summarised in Tables 1–6. The primary colonisation site in poultry is the ceca, where the *Campylobacter* population may reach 10^6–10^8 cfu/g (Meade et al., 2009). In humans, infection occurs predominantly in the small intestine. Several studies have reported enhanced human colonization capacity and virulence after passage through poultry (Stern et al., 1988; Cawthraw et al., 1996). It is thought that the invasion mechanisms in poultry and human cell lines are similar but not identical. For example, *C. jejuni* survive intracellularly in human T84 epithelial cells but cannot survive in primary chicken enterocytes (Van Deun et al., 2007). Regardless, colonization requires motility, adhesion, invasion and toxin production (Bang et al., 2003).

2.1. Motility

The motility system in *Campylobacter* requires flagella and a chemosensory system that drives flagellar movement based on the environmental conditions. The *Campylobacter* motility and chemotaxis factors are summarised in Tables 1 and 2.

2.1.1. Flagella

Motility is essential for survival under the different chemotactic conditions encountered in the gastrointestinal tract (Jagannathan and Penn, 2005) and for colonization of the small intestine (Guerry, 2007). *Campylobacter* show unusual motility, especially in viscous substances. This has been attributed to the presence of one or two polar flagella and the helical cell shape. The former provides propulsive torque and/or rotary cell movement, while the helical shape facilitates corkscrew rotation (Ferrero and Lee, 1988).

Table 1
Campylobacter motility factors.

Virulence factor(s)	Encoding gene(s)	References
FlaA, the major flagellin protein	*flaA*	Nachamkim et al., 1993; Wassenaar et al., 1993; Sommerlad and Hendrixson, 2007; Lertsethtakarn et al., 2011
FlaB, the major flagellin protein	*flaB*	Nachamkim et al., 1993; Wassenaar et al., 1993; Sommerlad and Hendrixson, 2007; Lertsethtakarn et al., 2011
FliF, hook–basal body protein	*fliF*	Carrillo et al., 2004
FliM & FliY, flagellar motor proteins	*fliM* & *fliY*	Nachamkim et al., 1993; Wassenaar et al., 1993; Sommerlad and Hendrixson, 2007; Lertsethtakarn et al., 2011
FlgI, P-ring in the peptidoglycan	*flgI*	
FlgH, L ring in the outer membrane	*flgH*	
FlgE & FliK, minor hook components	*flgE* & *fliK*	
σ^{28} promoter regulates *flaA* gene expression	*fliA*	Hendrixson, 2006
σ^{54} promoter regulates *flaB* gene expression	*rpoN*	Hendrixson, 2006
Proteins involved in flagellin *O*-linked glycosylation	*cj1321–cj1325/6*	Champion et al., 2005

Table 2
Campylobacter chemotaxis factors.

Virulence factor(s)	Encoding gene(s)	References
Chemotaxis proteins; Che A, B, R, V, W, & Z.	*cheA, cheB, cheR, cheV, cheW & che Z.*	Hamer et al., 2010
Methyl-accepting chemotaxis proteins (MCPs) also called transducer-like proteins	*tlp1, tlp4, tlp 10*	Marchant et al., 2002
CheY, response regulator controlling flagellar rotation	*cheY*	Hermans et al., 2011
Campylobacter energy taxis system proteins CetA (Tlp9) and CetB (Aer2)	*cetA & cetB*	Golden and Acheson, 2002
AI-2 biosynthesis enzyme	*luxS*	Quinones et al., 2009; Hermans et al., 2011
AfcB, MCP protein required for persistence in the cecum	*acfB*	Golden and Acheson, 2002

The flagellum is composed of a hook–basal body and the extracellular filament structural components. The hook–basal body includes; (1) a base embedded in the cytoplasm and inner membrane of the cell; (2) the periplasmic rod and associated ring structures and (3) the surface localized hook (see Lertsethtakarn et al. (2011) for a comprehensive description). The hook–basal body complex is composed of several different proteins including FliF (inner membrane MS ring that attaches the rod assembly to the cell membrane); FlhA, FlhB, FliO, FliP, FliQ and FliR (type 3 secretion system, T3SS), FliG, FliM, FliN and FliY (C ring with FliM and FliY serving as flagellar motor switch proteins (Carrillo et al., 2004)); MotA and MotB (motor components); FlgI (P ring in the peptidoglycan); FlgH (L ring in the outer membrane); FlgE and FliK (minor hook components) (see Fig. 1). The extracellular filament is composed of multimers of the protein flagellin including a major flagellin protein, FlaA (coded by *flaA*), and a minor flagellin protein, FlaB (coded by *flaB*) (Nachamkim et al., 1993; Wassenaar et al., 1993; Sommerlad and Hendrixson, 2007; Lertsethtakarn et al., 2011).

Transcription of the *flaA* gene, which is highly conserved among different *Campylobacter* isolates, is regulated by the σ^{28} promoter,

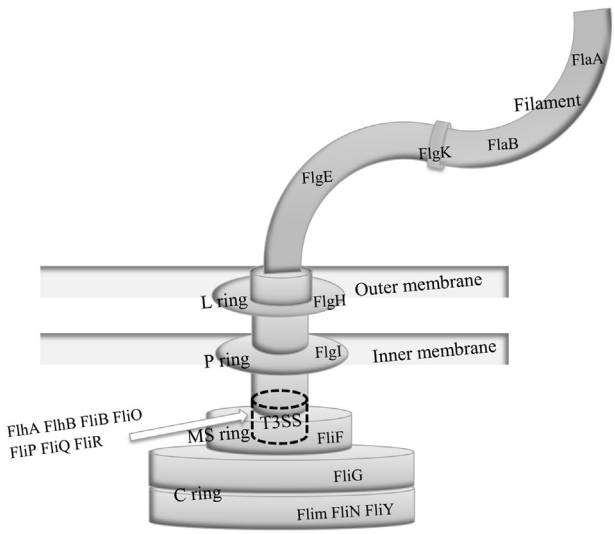

Fig. 1. Flagellar assembly showing the main components and associated proteins.