



Review

Host Factors in *Campylobacter jejuni* infection: A Review

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Infection with *C. jejuni* is usually self-limiting but has varied manifestations depending on the host and the host's geographical location, thus, prompting the importance of host immune responses in determining disease. Fucosylated sugars in breast milk have been demonstrated not only to inhibit *C. jejuni* binding and infection but also prevent diarrhoea in infants, whilst the bactericidal effect of human serum has long been demonstrated, underlining the importance of host innate responses in containment of infection with *C. jejuni*.

Key words: Immune responses, infection, *C. jejuni*, host factor, human serum

INTRODUCTION

Following ingestion, *C. jejuni* does not only have to survive the acidic environment of the stomach, but also has to bypass the mucus lining of the intestinal epithelium which are important barriers, the depletion of which leads to increased susceptibility to *Campylobacter* infection (Nakajima, 1999; Doorduyn et al., 2008; Tu, 2008). The epithelial lining plays a crucial role in microbial sensing to initiate appropriate innate immune responses such as the production of chemokines, cytokines, and antimicrobial peptides (Eckmann, 2005; Zilbauer, 2005b). Epithelial β -defensins, a family of host-defence peptides known to be modulated during *C. jejuni* infection and which have been demonstrated to be also present in the avian intestinal tract, play a very crucial role in mucosal innate defence through their chemotactic and bactericidal activity (Ganz 2003; Byrne, 2007).

Initiation of innate immunity is known to be mediated by the interaction of host pattern-recognition receptors (PRRs) with conserved microbial signature motifs called pathogen-associated molecular patterns (PAMPs) (Akira 2006, Sanderson and Walker 2007). The phylogenetically conserved Toll-like receptors (TLRs), which are expressed at the basolateral surface of the intestinal epithelium, constitute one of the commonest PRRs involved in flagella recognition and activation of host NF- κ B, a family of mammalian proteins that regulate transcription of pro-inflammatory genes involved in early host immunity

against infection (Ghosh, 1998; Gewirtz, 2001 and Hayashi 2001).

Immunological challenges

One of the early immunological challenges encountered by infecting *C. jejuni* is presumably the presence of these TLRs, which are present in most vertebrates including humans and chickens (Takeda, 2003; Young, 2007; Young, 2009). The stimulation of innate immune responses through TLR5 and TLR9, which are responsible for the recognition of primary flagellin structure and unmethylated CpG dinucleotides respectively, is known to be deficient in *C. jejuni* (Andersen 2003, Galan 2005, Watson 2005, Dalpke 2006, Johanesen 2006). However, a recent demonstration that mice deficient in MyD88, an important molecule downstream of TLRs, are more susceptible to *C. jejuni* infection has rekindled the belief that TLRs are important in the pathogenic mechanisms of campylobacters, providing host-immune defences (Watson 2007). This assertion is supported by previous but recent reports that NF- κ B is readily activated in *in vitro* models and that NF- κ B-gene deficient mice are also highly susceptible to *C. jejuni* infection (Jin, 2003; Jones, 2003; Fox, 2004; Zilbauer, 2005b; Chen, 2006; Johanesen, 2006 and Chen, 2009). Also, innate immunity has been shown to be partly mediated by other PRRs such as the nucleotide-binding oligomerization domain one

(NOD1), and the natural resistance-associated macrophage protein one (Nrampl) (Watson, 2007; Zhang, 2007). The interaction of *C. jejuni* with intestinal epithelial cells also results in the activation of MAP kinases, which in turn induce host responses such as the induction of interleukin 8 (IL-8) production by p38MAP kinases and extracellular regulated kinases (ERK) (Watson, 2005; MacCallum, 2005a). The interaction of *C. jejuni* surface protein, JlpA, with the heat shock protein 90 (Hsp90) of epithelial cells leads to the activation of both p38MAP and NF- κ B (Jin. S. 2003). In addition to TLR-mediated activation of NF- κ B, bacterial adhesion and invasion and the presence of CDT can stimulate IL-8 production (Hickey, 1999; Hickey, 2000; Hickey, 2005; Zheng, 2008).

The release of IL-8, and other pro-inflammatory cytokines such as interferon gamma (IFN γ), tumour necrosis factor alpha (TNF α), IL-2 and IL- β , in response to bacterial infection is not only considered to be crucial in bacterial clearance but also in the development of diarrhoea, through recruitment of polymorphonuclear leukocytes (PMNs), especially neutrophils to the site of local inflammation, recruitment of activated macrophages, inhibition of the absorptive functions of the intestinal epithelium and disruption of its cellular tight junctions (MacCallum, 2005b; Al-Banna, 2008; Zilbauer, 2008).

However, the degree of IL-8 induction has been shown to vary in *in vitro* models of infection and correlates well with pathological changes (MacCallum, 2006; Al-Banna, 2008).

The interaction of neutrophils (PMN) with infecting *C. jejuni* leads to phagocytosis of the bacterium resulting in the production of reactive oxygen species which, may lead to bacterial killing depending on the level of induction (Wooldridge and Ketley, 1997)(Wooldridge 1997). Monocytes and macrophages have long been shown to internalize and kill infecting *C. jejuni*, with the killing mediated by reactive nitrogen species (Al-Banna et al., 2008; Iovine et al., 2008; Wassenaar et al., 1997; Wooldridge and Ketley, 1997);(Wassenaar, 1997; Wassenaar, 1997; Wooldridge, 1997; Al-Banna, 2008; Iovine 2008). However, some studies have also demonstrated that a significant proportion of *C. jejuni*-infected monocytes do undergo apoptosis (Hickey et al., 2005; Siegesmund et al., 2004);(Siegesmund, 2004; Hickey, 2005). Furthermore, *C. jejuni* has been shown to survive in porcine and murine peritoneal macrophages for days, and this survival is attributed to the production of catalase by the bacterium (Day, 2000).

Recently, *C. jejuni* has been shown to also induce specific cell-mediated immune responses *in vitro* leading to the maturation of dendritic cells and secretion of associated pro-inflammatory cytokines (Hu et al., 2006a; Johanesen and Dwinell, 2006; Rathinam et al., 2008)(Johanesen, 2006; Hu, 2006a; Rathinam 2008). Johanesen et al. demonstrated an increased expression of CCL20, a chemo-attractant cytokine of dendritic cells, following exposure of T84 epithelial cell line to *C. jejuni*, which goes to buttress the involvement of cell-mediated immunity in *C. jejuni* pathogenesis (Johanesen and Dwinell, 2006);

(Johanesen, 2006).

In another study, Jones et al. have shown that maturation of dendritic cells is bacterial LOS-dependent and that it leads to internalization of *C. jejuni* (Jones et al., 2003);(Jones, 2003). Also, in an *in vivo* study by Fox and co-workers, it was demonstrated that IgG2a is produced in response to both the wild-type strain and a *cdtB* *C. jejuni* mutant, through Th1, and was responsible for clearance of the bacterium from infected mice (Fox et al., 2004);(Fox, 2004).

Although the significance of the protective effect of $\gamma\delta$ T-cells against *Campylobacter* infection is not known, it has been reported that non-protein extracts of *Campylobacter* can induce *in vitro* expansion of these (Van Rhijn et al., 2003)(Van Rhijn, 2003).

Humoral response

Several studies have described humoral immune responses following human infections with *C. jejuni* (Blaser & Duncan, 1984; Blaser et al., 1985a; Blaser et al., 1986; Lane et al., 1987; Martin et al., 1989; Mizuno et al., 1985)(Blaser 1984, Mizuno, 1985; Blaser, 1985a; Blaser, 1986; Lane, 1987; Martin, 1989). Likewise, similar responses have been reported in several animal models including monkeys, rabbits, hamsters and mice (Humphrey, 1985; Russell, 1989; Russel, 1994; Rangarajan, 2007).

Immune response

This immune response has been attributed to some components of the bacterium, such as the flagella, MOMP, LOS, CDT and outer membrane proteins (Omps) (Mills, 1984; Nachamkin, 1989; Guerry, 2000; Abuoun, 2005; Huang, 2007).

Infection with *C. jejuni* has also been reported to generate a secretory immunoglobulin A (sIgA) in both humans and experimental rabbits (Burr et al., 1988)(Burr 1988, Burr 2005). In infants, *C. jejuni* infections result in the generation of low levels of IgA, IgG and IgM, which is thought to be due to the presence of maternal antibodies (Ruiz-Palacios, 1990; Young, 2007). Antibodies produced as a result of *C. jejuni* infection have long been shown to be (Dolby 1986, McSweeney 1987; Black 1988; Ruiz-Palacios, 1990). A pentaglobulin preparation containing *C. jejuni* specific IgM is reported to have been used to successfully treat hypoglobulinemic patients who were suffering from chronic campylobacteriosis (Borleffs et al., 1993)(Borleffs 1993).

Conclusion

Children in developing countries and persons who consume high amounts of raw milk tend to have high levels of IgG which is thought to protect them against bloody diarrhoea (Blaser, 1984; Blaser, 1985a; Blaser, 1986; Blaser 1997).

Following infection, the level of IgG is thought to persist longer than IgA or IgM levels, which affirms the superior

protective effect of the former (Cawthraw et al, 2002; Russell et al, 1989);(Russell, 1989; Russel, 1993; Russel, 1994; Cawthraw, 2002).

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