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Review

The immunobiology of *Campylobacter jejuni*: Innate immunity and autoimmune diseases

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ABSTRACT

The Gram-negative bacterium *Campylobacter jejuni* causes gastroenteritis and Guillain-Barré syndrome in humans. Recent advances in the immunobiology of *C. jejuni* have been made. This review summarizes *C. jejuni*-binding innate receptors and highlights the role of innate immunity in autoimmune diseases. This human pathogen produces a variety of glycoconjugates, including human ganglioside-like determinants and multiple activators of Toll-like receptors (TLRs). Furthermore, *C. jejuni* targets MyD88, NLRP3 inflammasome, TIR-domain-containing adapter-inducing interferon-β (TRIF), sialic acid-binding immunoglobulin-like lectins (Siglecs), macrophage galactose-type lectin (MGL), and immunoglobulin-like receptors (TREM2, LMIR5/CD300b). The roles of these innate receptors and signaling molecules have been extensively studied. MyD88-mediated TLR activation or inflammasome-dependent IL-1β secretion is essential for autoimmune induction. TRIF mediates the production of type I interferons that promote humoral immune responses and immunoglobulin class-switching. Siglec-1 and Siglec-7 interact directly with gangliosides. Siglec-1 activation enhances phagocytosis and inflammatory responses. MGL internalizes GalNAc-containing glycoconjugates. TREM2 is well-known for its role in phagocytosis. LMIR5 recognizes *C. jejuni* components and endogenous sulfoglycolipids. Several lines of evidence from animal models of autoimmune diseases suggest that simultaneous activation of innate immunity in the presence of autoreactive lymphocytes or antigen mimicry may link *C. jejuni* to immunopathology.

Contents

1. Introduction

Campylobacter jejuni glycosylation, capsule polysaccharides (CPS), lipooligosaccharide (LOS), and sialylation are the major sources of glycoconjugates capable of modulating host immunity. Two protein–glycosylation systems exist in this human pathogen; *O*-linked glycosylation modifies serine or threonine residues on flagellin, while *N*-linked glycosylation modifies asparagine residues on many proteins (Nothaft and Szymanski, 2010). A lack of *N*-linked glycosylation enhances inflammatory responses (van Sorge et al., 2009). CPS is known as the serodeterminant molecule as CPS-deficient *C. jejuni* strains are not serotypeable by the Penner scheme (Karlyshev et al., 2000). CPS seems to inhibit inflammatory

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Table 1
C. jejuni-sensing receptors.

Receptors[a]	*C. jejuni*	Signaling	Outcomes	Methods[b]	Refs.
mTLR2	Intact bacteria	MyD88	IL-6, IL-12, TNF	TLR2$^{-/-}$ DC	Rathinam et al. (2009)
mTLR2	Glycoconjugates	MyD88, NF-κB	IL-6, IL-12	TLR2$^{-/-}$ MQ, TLR2 reporter	Phongsisay et al. (2015a)
mTLR4	Intact bacteria	MyD88, TRIF	IL-6, IL-12, TNF	TLR4$^{-/-}$ DC, TRIF$^{-/-}$ DC	Rathinam et al. (2009)
mTLR4	Glycoconjugates	MyD88, NF-κB	IL-6, IL-12	TLR4$^{-/-}$ MQ, TLR4 reporter	Phongsisay et al. (2015a)
hSiglec-1	Whole cells	ND	Phagocytosis,IL-6	Sn-expressing MQ	Heikema et al. (2013)
mSiglec-1	Sialylated bacteria	ND	Phagocytosis, TNF-α, IFN-β	Sn-expressing MQ, Sn$^{-/-}$ mice	Klaas et al. (2012)
hSiglec-7	LOS, intact bacteria	ND	ND	Direct binding	Avril et al. (2006)
hSiglec-10	Flagellum	p38	IL-10	Siglec10-expressing cells	Stephenson et al. (2014)
hMGL	Glycoproteins, LOS	ND	ND	Direct binding	van Sorge et al. (2009)
mTREM2	Whole cell lysate	DAP12	ND	LMIR5-Fc, TREM2 reporter	Phongsisay (2015)
mLMIR5	Proteins, RNA-associated proteins, glycoconjugates	DAP12	ND	LMIR5-Fc, LMIR5 reporter	Phongsisay (2015)

[a] m, mouse receptor; h, human receptor.
[b] DC, dendritic cells, MQ, macrophages; ND, not determined.

responses; a CPS-lacking *C. jejuni* mutant induced higher cytokine production when compared with the wild type (Maue et al., 2013). LOS is a surface glycolipid consisting of an oligosaccharide moiety and a lipid A. LOS components without *O*-antigen have long been recognized as low-molecular-weight bands. However, *C. jejuni* strains have recently been reported to produce high-molecular-weight components that appear as ladder-like bands similar to the lipopolysaccharide (LPS) of other Gram-negative bacteria (Kovács et al., 2014). The lipid A possesses endotoxic properties and it is a potent activator of inflammation. Structural variations are reported in the oligosaccharide moiety, the disaccharide lipid A backbone, and the lipid A phosphorylation. This variation affects inflammatory potency and cellular activation (Stephenson et al., 2013). Sialylation is reported in the oligosaccharide of LOS. LOS sialylation increases bacterial uptake and cytokine production by immune cells (Huizinga et al., 2012). In particular *C. jejuni* strains, the sialylated oligosaccharide is structurally similar to human gangliosides. This antigen mimicry has been proposed as the cause of axonal Guillain-Barré syndrome (GBS) characterized by the presence of anti-ganglioside antibodies and weakness of limbs (Yuki et al., 2004). Innate immunity recognizes a variety of microorganisms through immunoreceptors. These receptors include peptidoglycan-sensing receptors, dsRNA sensors, dsDNA sensors, inflammasomes, ITAM or ITIM-bearing receptors, endocytic receptors, Toll-like receptors (TLRs), immunoglobulin-like receptors, and C-type lectin receptors. A number of receptors are activated through several signaling molecules. For instance, TIR-domain-containing adapter-inducing interferon-β (TRIF) and MyD88 are adaptor proteins of TLRs (Akira and Takeda, 2004). ITAM-bearing adaptor proteins (DAP12, FcRγ) and caspase recruitment domain-containing protein 9 (CARD9) are downstream signaling molecules associated with a number of C-type lectin and immunoglobulin-like receptors (Hara et al., 2007; Yamanishi et al., 2008; Miyake et al., 2013; Yonekawa et al., 2014).

Identification of *C. jejuni*-sensing receptors has received great attention as these receptors may explain the link between *C. jejuni* and immunopathology. The pathophysiology of *C. jejuni* and the clinical association between *C. jejuni* and GBS have been extensively reviewed (Young et al., 2007; Kuwabara and Yuki, 2013). This review summarizes *C. jejuni*-binding receptors and highlights the role of innate immunity in autoimmune diseases. Toll-like receptors, sialic-acid binding immunoglobulin-like lectins (Siglecs), NLRP3 inflammasome, C-type lectin receptors, and immunoglobulin-like receptors are included in this review. *C. jejuni*-binding innate receptors are summarized in Table 1 and Fig. 1.

2. Toll-like receptors

TLRs play an important role in innate immunity by recognizing a variety of self- and non-self components. For example, TLR2, TLR3, TLR4, TLR5, and TLR9 recognize fungal zymosan, viral RNA, LPS, flagellin, and CpG oligodeoxynucleotide, respectively. TLR4 is also activated by Mrp8, Mrp14, HMGB1, histones, and cold-inducible RNA-binding protein (Akira and Takeda, 2004; Vogl et al., 2007; Yang et al., 2010; Xu et al., 2011; Qiang et al., 2013). The adaptor protein MyD88 is essential for most TLRs, except TLR3. Upon ligand stimulation, other than TLR3 activation results various inflammatory responses via MyD88-NF-κB signaling pathway. On the other hand, TLR3 particularly mediates the production of type I interferons via TRIF-IRF pathway. TLR4 activates not only MyD88-NF-κB but also TRIF-IRF pathway (Akira and Takeda, 2004).

The role of TLRs in autoimmune diseases is well established. TLR4 activation is crucial in the development of autoreactive CD8+ T cells (Loser et al., 2010). The loss of TLR4 in CD4+ T cells abrogates the induction of experimental autoimmune encephalitis (EAE), mainly through blunted Th17 and Th1 responses (Reynolds et al., 2012). MyD88-, TLR2-, or TLR9-deficient mice are resistant to EAE (Miranda-Hernandez et al., 2011). TLR2 and TLR4 are critical for autoantibody production in the mouse model of autoimmune disease (Lartigue et al., 2009).

An intact *C. jejuni* is reported to activate MyD88 and TRIF in mouse dendritic cells (DCs) (Rathinam et al., 2009). In the absence of TLR2, TLR4, MyD88, and TRIF, *C. jejuni*-infected DCs showed a marked reduction of inflammatory cytokines, major histocompatibility complex class II, costimulatory molecules, and Th1-priming capacity. Furthermore, *C. jejuni* induced IRF3 phosphorylation and IFN-β secretion in a TLR4-TRIF-dependent manner (Rathinam et al., 2009).

Little is known about the *C. jejuni* components that possess inflammatory properties; LOS targets human TLR4 (Stephenson et al., 2013), while *C. jejuni* flagellin and DNA do not activate TLR5 and TLR9, respectively (Andersen-Nissen et al., 2005; de Zoete et al., 2010). Phongsisay et al. (2015a) have attempted to identify the *C. jejuni* components capable of inducing inflammatory responses using a combination of enzymatic treatments, SDS-PAGE-based purification, and NF-κB reporter cells in human monocytes. LPS is solely a proteinase K-resistant glycoconjugate in *Escherichia coli*. In contrast, *C. jejuni* possesses at least five glycoconjugates capable of inducing NF-κB activation (Phongsisay et al., 2015a). The first glycoconjugate appears as an approximately 150 kDa ladder-like band. This component is designated as CjκB150 according to its molecular weight on SDS-PAGE. The second glycoconjugate is a ladder-like band between 30 and 50 kDa (CjκB30–50). The identity of CjκB150 and CjκB30–50 are currently unknown. Another three

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