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Chapter

The Role of Immune Response and Microbiota on Campylobacteriosis

Ying Fu, Tahrir Alenezi, Ayidh Almansour, Hong Wang, Zhenquan Jia and Xiaolun Sun

Abstract

Million cases of campylobacteriosis and complications of post-*Campylobacter jejuni* infection occur every year around the world with huge life losses and economic burdens of billions of dollars. Few therapy options, such as antibiotics, are available to relieve severe cases of the enteritis. The slow progression on new intervention discovery and application is partially resulted from limited mechanistic understanding on campylobacteriosis pathogenesis. As a type of intestinal disorders, campylobacteriosis shares many common features with other intestinal diseases such as inflammatory bowel diseases (IBD) and *Clostridium difficile* infection. In pace with the advancement of the gastroenterology field, a large body of knowledge is accumulating on the factors influencing campylobacteriosis onset, development, and outcomes, including host immune response, intestinal microbiota, and its metabolites. In this chapter, we review the intestinal immune system, intestinal microbiome, and microbiome modulation of inflammation in the development of campylobacteriosis. The interplay between immunity, microbiota, and its metabolites may play essential roles on campylobacteriosis pathogenesis and the finding on the interaction may lead to new prevention and treatment options. The purpose of this chapter is to provide updated knowledge on the role of host–microbe interaction and the therapeutic potential on campylobacteriosis.

Keywords: colitis, infection, adaptive immunity, innate immunity, microbial metabolite, bile acids

1. Introduction

Campylobacter enteritis (also known as campylobacteriosis) is defined as an infection of the intestines that is manifested in the form of acute diarrhea followed by pain in abdomen, fever as well as other constitutional clinical indications [1]. Campylobacteriosis is a common foodborne pathogen disease worldwide caused by *Campylobacter jejuni* [2]. *C. jejuni* is a Gram-negative, microaerobic bacterium. Because of the large consumption and industrialized production of animal meat, the main reservoir of *C. jejuni* is food animals such as chickens and turkeys. *Campylobacter* is one of the most frequent causes of foodborne bacterial pathogen, particularly in developed countries. *C. jejuni* and *C. coli* are the foremost causes of infections in the vast majority of population [3]. According to CDC's report, 24% raw chicken meat carried *C. jejuni* [4]. Around 1.5 million cases reported in USA every year [5] and causing $6.9 billion losses annually [6].

C. jejuni is able to establish infection in the intestine with ingestion of minimum 500 viable bacteria, but the infection efficiency is influenced by host antibacterial defenses such as gut immune system and the intestinal commensal microbes [7]. The innate and adaptive immunity in gut actively surveils the luminal microbes, processes the intestinal cues, and establishes defense actions, resulting in constant gastrointestinal homeostasis [8]. The complex gut resident microbes live on and inside the host including bacteria, fungi, protozoa, viruses, and their metabolic products [9]. The gut microbes are important participants for food digestion, fermentation, and energy accommodation of intestinal tract [10]. During physiological process, metabolites, such as short chain fatty acid, bile acid, vitamins, and amino acids, are produced. The microbes, along with their metabolites play important roles in keeping the homeostasis of gastrointestinal immunity, and affecting their resistance to the invasion of pathogens [11]. In the following sections, we will have a detailed discussion on gut immunity, resident microbes, and their role on campylobacteriosis.

2. Intestinal immunity on campylobacteriosis

The immune system is comprised of a complex network of biological molecules and activities in organs, tissues, and cells to protect an organism against foreign substances or microbes (**Figure 1**). The immunity is generally categorized into two subsystems of innate and adaptive immunity [12]. The innate immunity initiates a quick immune response [13], while the adaptive immunity generates a comprehensive and long-lasting immune defense [12]. These two immune branches work closely together to defense host against the encountered foreign substances or microbes. The intestinal immunity is highly involved with *C. jejuni*-induced colitis. *C. jejuni*–induced severe campylobacteriosis in *Il10*$^{-/-}$ mice as showed by extensive intestinal immune cell infiltration, epithelial damage, goblet cell depletion and crypt hyperplasia and abscesses compared with uninfected mice [14]. In this section, we will briefly review recent advancement of intestinal immunity and campylobacteriosis.

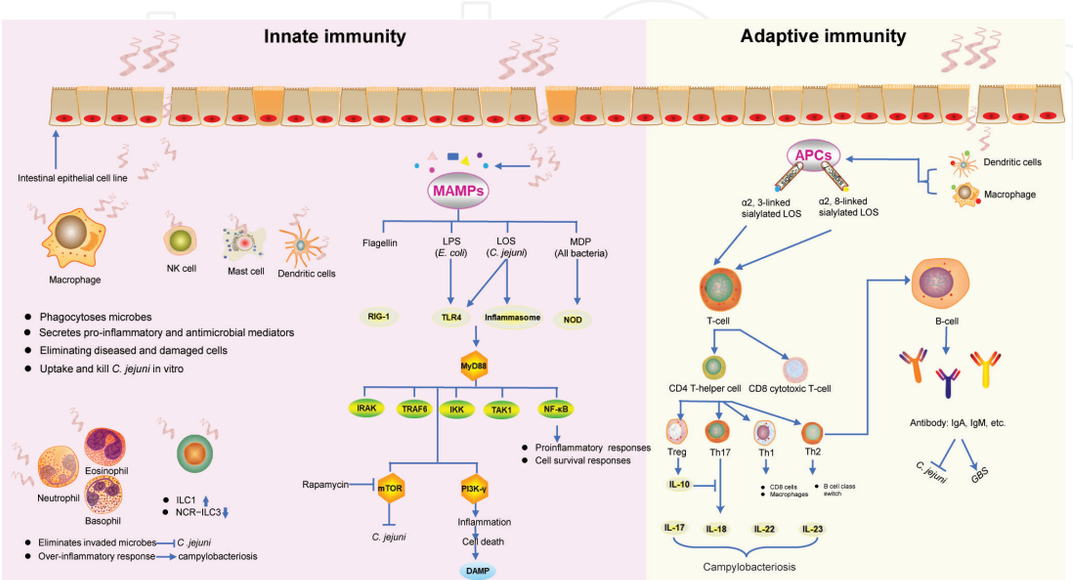

Figure 1.
Schematic illustration of the role of innate (left side) and adaptive (right side) immunity in campylobacteriosis.

2.1 Intestinal immunity and campylobacteriosis

In the gastrointestinal tract, the innate immunity is consisted of innate cells and soluble molecules, which are an important defense mechanism against foreign substances or microbes. The cellular innate immunity is consisted of various types of cells, including intestinal epithelial cell (IEC), granulocyte (neutrophil, basophil, and eosinophil,) dendritic cell (DC), macrophage, natural killer cell (NK), master cell, and innate lymphoid cell (ILC), and γδ T cell [15]. Only a single layer of IEC separates nearly sterile internal intestinal tissue from microbe-rich intestinal lumen, hence the integrity of IEC is essential for intestinal health. Notably, IEC line breakdown is often implicated in various intestinal disorders such as IBD [16], irritable bowel syndrome (IBS) [17], colorectal cancer [18], and *C. difficile* infection [19]. The destruction of IEC line and tissue upon invasion of *C. jejuni* [20] clearly demonstrates the important role of the epithelial cells. The innate effector cell of scavenging macrophage phagocytoses microbes and secretes both pro-inflammatory and antimicrobial mediators [21]. In addition, macrophage is essential for eliminating diseased and damaged cells through its programmed cell death. Macrophage uptakes and kills *C. jejuni in vitro* [22], although the role of macrophage in campylobacteriosis remains to be determined. Neutrophil is the most abundant type of granulocytes and consists of 40% to 70% of all white blood cells in humans [23]. Although neutrophil eliminates invaded microbes, the over-inflammatory response of neutrophil is responsible for the campylobacteriosis in a *Il10*$^{-/-}$ mouse model [24]. *C. jejuni*-induced colitis increases ILC1 (50% vs. 18%) but decreases NCR − ILC3 (13% vs. 43%) in the colonic lamina propria of germ free *Il10*$^{-/-}$ mice, compared to uninfected mice [25]. Effort is needed to investigate the role of various innate cells on campylobacteriosis pathogenesis.

At the molecular level, the innate cells recognize the microbes of their microbial-associated molecular patterns (MAMPs), such as lipopolysaccharides (LPS) and flagellin. MAMP is a component of a microbe and is sensed by innate cellular pathogen recognition receptors (PRRs), such as toll-like receptors (TLRs), nucleotide oligomerization domain (NOD) like receptors (NLRs), and retinoic acid inducible gene-I (RIG-I) like receptors (RLRs) [26, 27]. Previous articles have comprehensively reviewed the interaction between MAMP and PRR [28], hence we will not devote too much on them. Relevant to the topics of this chapter, LPS is expressed on the surface of Gram-negative bacteria such as *E. coli*, and it is recognized by TLR4 at the innate cell surface. *C. jejuni* expresses lipo-oligosaccharide (LOS) instead of LPS [29] and LOS is possibly recognized by TLR4 in DC and *Il10*$^{-/-}$ mouse model [20, 30]. Muramyl dipeptide (MDP) is the minimal bioactive peptidoglycan motif common to all bacteria and is sensed by NOD2 in innate cytoplasm. Microbiota-disturbed *Il10*$^{-/-}$; *Nod2*$^{-/-}$ mice are susceptible to *C. jejuni*-induced colitis compared to *Il10*$^{-/-}$ mice [31], suggesting the role of NOD2 in host shown preventive mechanism against the pathogen. It is much needed to investigate various PRRs on detecting *C. jejuni* infection and to elicit immune response.

After trigged by PRRs detecting MAMP, innate response of a network of signaling pathways are activated, including TLR-MyD88/TRIF and inflammasome. MyD88 is a downstream adaptor protein of TLR and is essential for the signal transduction of the TLR signaling pathway [32]. The TLR signaling pathway is classified into either MyD88-dependent or MyD88-independent. With the exception of TLR3, all downstream signaling pathways of TLRs mediate through MyD88 [33]. For MyD88 dependent pathway, TLR signaling recruits and activates a number of molecules, including IRAK, TRAF6, TAK1, IKK, and NF-κB [32]. The TLR/Myd88/NF-κB signaling pathway then induces proinflammatory and cell survival responses. NF-κB signaling is activated in *C. jejuni*-induced colitis using germ free

Il10$^{-/-}$; NF-κB^{EGFP} mouse model. mTOR signaling is a downstream target of MyD88 and mediates *C jejuni*-induced colitis in *Il10*$^{-/-}$ and *Il10*$^{-/-}$; *Rag2*$^{-/-}$ mice, suggesting independence of T-cell activation [14, 24]. Blocking mTOR signaling with pharmacological inhibitor rapamycin attenuates *C jejuni*-induced intestinal inflammation, immune cell infiltration and the pathogen invasion, while rapamycin increases splenocyte autophagy [14]. In addition, *C. jejuni*–induced MyD88 downstream target PI3K-γ signaling mediates intestinal inflammation in *Il10*$^{-/-}$ mice through modulating neutrophil migration/infiltration into intestinal lamina propria [24]. During inflammation, damaged or dying cells release endogenous danger molecules called damage-associated molecular pattern (DAMP) such as high-mobility group box 1 (HMGB1), S100 proteins, and heat shock proteins (HSPs). The DAMP is sensed by TLR and inflammasome and is investigated extensively in non-infectious inflammation disorders [34]. Inflammasome is responsible for processing proIL1β and proIL18 into active forms [35]. It would not be surprised to find that DAMP-induced inflammation in *C. jejuni*-induced colitis, hence such work would yield important leads to understanding campylobacteriosis pathogenesis.

2.2 Intestinal adaptive immunity and campylobacteriosis

Despite the effective, fast, and general/non-specific response of innate immunity against infection, adaptive immunity is often developed in vertebrate animals, particularly in the case of unresolved innate response. With the assistance of innate immunity, the adaptive immunity of lymphocytes recognize and remember a foreign substance's or pathogen's unique antigens and builds an antigen-specific response to eliminate it [12]. Two major lineages of T and B lymphocytes are generated in the thymus and the bone marrow or the avian bursa of Fabricius [36]. The adaptive immunity mounts two types of activities: B cell mediated antibody responses, and T cell mediated immune response. DC, B-cell, and macrophage express specific "co-stimulatory" ligands recognized by co-stimulatory receptors on T cells, and are named antigen-presenting cells (APCs) for T cell activation. During the early developmental stages, B lymphocyte progenitor cells make somatic hypermutation for specific antibody, while T and B cells rearrange different sets of immunoglobulin (Ig) variable (V), diversity (D), and joining (J) gene segments to make the antigen binding regions of the T cell receptors (TCRs) and B cell receptors (BCRs) [37]. *Campylobacter* infection-induced Guillain-Barré syndrome (GBS), an autoimmune disease, demonstrates the implication of adaptive immunity in the pathogen infection.

T cells are grouped into two types based on the surface antigens: CD4-expressing T-helper cells, and CD8-expressing cytotoxic T-cells [38]. It remains elusive the role of CD8 cells in campylobacteriosis, but accumulating evidence supports the notion on the important role of CD4 cells in campylobacteriosis pathogenesis. The major intestinal CD4$^+$ T cells are T help cell 1 (Th1), Th17, and regulatory T cell (Treg, Foxp3-expressing) cells, although Th2, Th9, Th22, follicular helper T (Tfh), iTreg, and type 1 regulatory T cell (Tr1) are present [39, 40]. The adaptive immunity is actively influenced by innate immunity. In gut lamina propria, intestinal innate tolerogenic CD103$^+$ DCs induce FoxP3+ Tregs by stimulating CCR7 and integrin-$\alpha_{IV}\beta_7$ on T cells resided in mesenteric lymph nodes [41–43]. The differential interaction between *Campylobacter* LOS and siglec-7 receptors on APC cell-surface influences the fate of naïve CD4 cells into different type of effector Th cells [44, 45]. Specifically, siglec-7 receptors on APC binds with α2, 8-linked sialylated LOS induces the Th1 polarization, while its interaction with α2, 3-linked sialic acid induces a Th2 development [45]. Generally, Th1 cells activate more cytotoxic CD8

cells and macrophages to enhance immunity against the invading or intracellular microbes, while Th2 cells mediate class switching of B-cells to eliminate the extracellular microbes [38]. Besides Th1 and Th2 cells, Th17, Th22, and Treg may also be induced in campylobacteriosis as evidenced by the elevated cytokine markers of IL-17, IL-18, IL-22, IL-23, and IL-10 in patients' serum following infection with *Campylobacter* [26, 46].

After Th2 cell activation, B-cells are induced to produce antibody (Ab) against *Campylobacter* infection. At 7 days post-infection (acute phase), blood Abs, IgA and IgM increase in serum [47]. From 1 week up to 1-year post-infection (convalescent phase), anti-*Campylobacter* Ab is detectable in serum and saliva of campylobacteriosis patients and could protect the subjects against subsequent *Campylobacter* infection [48, 49]. Similarly, IgA and IgM are persistent in campylobacteriosis patients for up to 20 days or 2 months post-infection. The downside to the adaptive humoral response is the incidence of GBS. *Campylobacter* often alters its LOS outer core to mimic human neuronal gangliosides for escaping from the host immune system but resulting in GBS [50]. α2, 3-linked sialic acid in *C. jejuni* LOS is one of the culprits. Developing effective vaccine or monoclonal antibody to control *C. jejuni* infection is, therefore, imminent.

3. Intestinal microbiome and campylobacteriosis

Human body, particularly gastrointestinal tract, inhabits trillions of diverse microbes including bacteria, archaea, virus, and eukarya [51]. These microbes called microbiota (**Figure 2**), and their metabolic activities and metabolites are collectively named microbiome [52]. The microbiota demonstrates a complex and diverse phylogeny of notable microbial species [53–55]. The human microbiota is comprised of 2172 prokaryotic species and the main phyla are Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria [56]. The inhabitant gut microbiota influences important biological processes, such as metabolism of food, production of fat and vitamins, activation of angiogenesis as well as safeguard against adversary pathogens [53, 54]. Relevant to the topic of this chapter, the colonization of gut microbiota effectively inhibits the colonization and excessive growth of

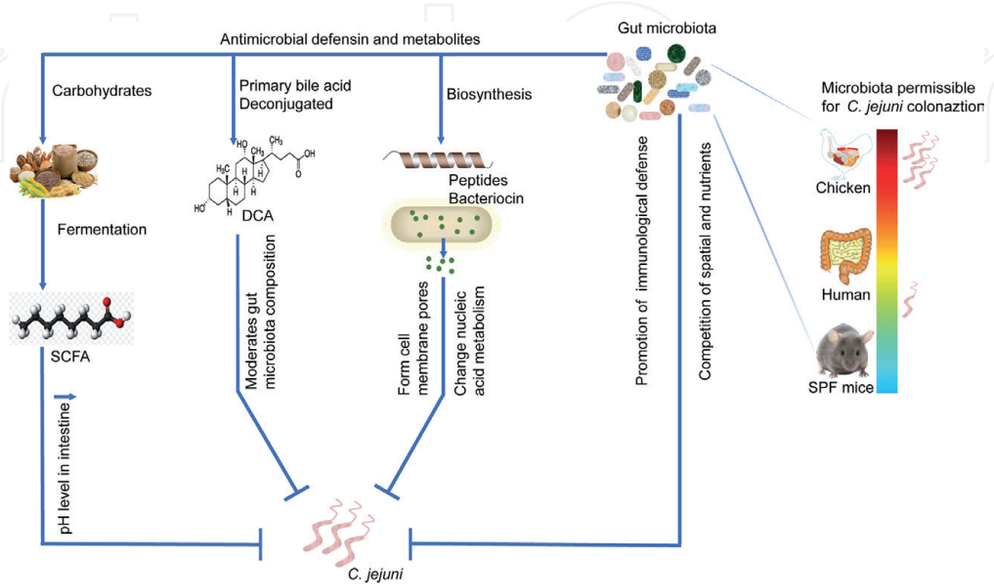

Figure 2.
Schematic illustration of the role of microbiota and its metabolites in campylobacteriosis.

potential pathogenic microbes, called colonization resistance [55]. The colonization resistance is through various mechanisms including direct competition of spatial and nutrients, production of antimicrobial defensin and metabolites, and indirect inhibition via stimulation of innate and adaptive immunity [57]. Certain microbiota phyla reduction is associated with an abolished biological colonization resistance [7, 58]. The colonization resistance, therefore, prevents pathogen attachment to the respective target site, depletes nutrients, and blocks virulence expression.

During its metabolism of nutrients, microbiota synthesizes varied range of metabolites and related small molecules [59–62]. It is recognized that the microbiota metabolites are absorbed across the gastrointestinal tract in circulation and impact host physiology [63–65]. Accumulating findings strongly support the important role of microbiota metabolites against gut pathogens. One example of the metabolite is short-chain fatty acids (SCFA). SCFA is fermented from carbohydrates (e.g., starch and fiber) and influences the gut microbiota community by reducing luminal pH level [66–69]. Another abundant microbiota metabolite is bile acid. Bile acids produced in the liver are excreted into the intestine as conjugated (taurine or glycine) forms to facilitate in digestion of dietary lipids. The bile acids are deconjugated in small intestine by bile salt hydrolases (BSH) [70] and absorbed up to 95% along intestinal line through enterohepatic cycle [71]. Furthermore, microbiota produces bacterial toxic and short peptides (e.g. bacteriocin) and bacterial toxins to inhibit the growth and colonization of other species [72]. The bacterial toxic peptides are categorized into those produced by Gram-negative bacteria (mostly by *Enterobacteriaceae*) and those produced by Gram-positive bacteria (lactic acid bacteria and some *Streptococcus* species) [73, 74]. The peptides are further classified into subgroups based on molecular weight, such as microcins (lower molecular weight peptides) and colicins (higher molecular weight proteins). The inhibition mechanism of bacteriocin is to change nucleic acid metabolism and to form cell membrane pores for eliminating other bacteria [75–78]. In this section, we will briefly review recent advancement on the interaction of microbiome and campylobacteriosis.

3.1 Microbiota and campylobacteriosis

To colonize in the gut, *C. jejuni* has to overcome numerous hurdles and endures in diverse environments. With minimum 500 viable bacteria, the pathogen has to establish in the intestine against host antibacterial defenses such as the intestinal bile acids and the intestinal microbiota [7]. The pathogenesis of *Campylobacter*-induced enteritis remains elusive because of lacking reliable animal models. Notably, *C. jejuni* is often colonized in birds without any pathological symptom [79, 80], while specific pathogen free mice, but not germ-free mice, are resistant to the pathogen colonization [24, 81]. Humans are susceptible to *C. jejuni*-induced enteritis, but the pathogen is often cleared within 1 to 2 weeks [82]. The reason why *C. jejuni* colonizes animals differentially remains elusive. Because the intestinal microbiota is different between animals, it is possible the gut microbiota influences bacterial pathogen colonization [55].

Chickens are susceptible to *C. jejuni* asymptomatic colonization and their microbiota could be friendly to *C. jejuni* infection. In 35-day old broiler chickens, families *Lactobacillaceae* and *Clostridiaceae* in the ileum and *Lachnospiraceae* and *Ruminococcaceae* in ceca are dominant, while genera *Ruminococcus* and *Oscillospira* account for 35% in ceca operational taxonomic units (OTUs) [80]. In a field study of 35-day old broiler chickens at four farms in Italy, the relative abundance of

class *Clostridiales* is higher in caeca of *Campylobacter*-negative farms than positive farms, while *Bacteroidales* is the opposite (80.0% vs. 65.7%) [83]. In 56-day old broiler chickens, *C. jejuni* colonization is associated with reduced genera abundance of *Corynebacterium* and *Lactobacillus* but increased genera *Ruminococcaceae* and *Streptococcus* [84]. The authors also found that *C. jejuni* colonization is positively associated with genera *Escherichia*, *Alistipes*, *Enterococcus*, *Bacteroides*, *Shigella*, *Gallibacterium*, *Campylobacter*, *Faecalibacterium*, *Blautia*, *Enterobacter* and *Clostridium*. In mice, two genera of *Clostridium sensu stricto* and *Enterococcus* are associated with mice susceptible to *C. jejuni*-induced colitis in a microbiota transplantation model [85]. Ampicillin treatment increases cecal genus *Barnesiella* but reduced *Clostridium XIVa* in the microbiota of *C. jejuni*-susceptible mice [86]. The abundance of *E. coli* is positive associated with *C. jejuni* colonization in mice [87]. Human campylobacteriosis patients have an increased abundance of genera *Escherichia*, *Bacteroidetes*, *Phascolarctobacterium*, and *Streptococcus* in stool [3]. Comparably, microbiota sequencing data from cross-sectional IBD patients showed that IBD is associated with dysbiosis characterizing by reduced gut bacterial diversity, together with increased genera *Fusobacterium*, *Escherichia, Faecalibacterium*, *Roseburia, Ruminococcaceae*, *Peptostreptococcaceae, Christensenellaceae*, and *Collinsella* [88]. The changes in the gut microbiota of IBD patients show an increase in facultative anaerobes, including *Escherichia coli* [89], and a decrease in obligately anaerobic [90]. IBD patients with active disease have increased gut *Enterococcus, Fusobacterium, Haemophilus, Megasphaera, Campylobacter*, while *Roseburia, Christensenellaceae, Oscillibacter, and Odoribacter* are enriched in the gut of IBD patients with inactive disease [88]. Although increasing evidence supports the role of microbiota promoting *C. jejuni* infection or other enteritis, additional studies are much needed.

On the other hand, SPF mice are resistant to *C. jejuni* colonization and their microbiota could be hostile to *C. jejuni* colonization. Through mining 16S DNA sequencing datasets, the core microbiota of healthy mice in cecum is found to be comprised of 37 genera, including *Anaerostipes, Parabacteroides, Anaerotruncus, Oscillibacter, Clostridium XlVb, Flavonifractor, Bacteroides, Barnesiella, Alistipes, Helicobacter, Saccharibacteria, Prevotella, Lachnoanaerobaculum, Lactobacillus, Intestinimonas, Roseburia, Alloprevotella, Rikenella, Enterorhabdus, Erysipelotric haceae_incertae_sedis, Eggerthella, Allobaculum, Lachnospiracea_incertae_sedis, Pseudoflavonifractor, Bifidobacterium, Marvinbryantia, Mucispirillum, Clostridium XIVa, Blautia, Anaerofilum, Parasutterella, Odoribacter, Olsenella, Turicibacter, Gordonibacter, Ruminococcus,* and *Acetatifactor* [91]. Eight genera of *Clostridium XI, Oscillibacter, Bifidobacterium, Butyricicoccus, Hydrogenoanaerobacterium, Lactobacillus, Roseburia,* and *Coprobacillus* are increased in the microbiota of *C. jejuni*-resistant mice [85]. Supplementation of *Bifidobacteria* and *Lactobacillus* species has been shown to reduce the colonization of *Campylobacter* in birds [92–95]. The probiotics against *Campylobacter* colonization are through promotion of immunological defense mechanisms such as stimulation of defensins and interleukins as well as alteration of integrity of epithelial cell barrier [96].

In human subjects with *Campylobacter*-negative, the abundance of genera *Clostridiales*, unclassified *Lachnospiraceae*, and *Anaerovorax* are increased [3]. Comparably, the *Campylobacter*-negative individuals showed increased abundance of family *Lachnospiraceae,* particularly its two genera *Dorea* and *Coprococcus* [97]. People who consume plant-based low fat and polysaccharide rich diet are more resistant to *C. jejuni* infection compared to individuals consuming western diet [98]. Hence, increasing studies are being performed to investigate the role of microbiota against *C. jejuni* infection.

3.2 Microbial metabolites and campylobacteriosis

The questions following section 3.2 are how microbiota facilitates or reduces *C. jejuni* infection. Besides direct inhibition by competition of space and nutrients [53, 54], microbiota metabolites may exert indirect antagonism against *C. jejuni*. The intestinal microbiota generates a variety of bioactive metabolites after metabolizing nutrients from diets and host secretions. A few data are available on the relationship of microbiota metabolites and *C. jejuni* infection, but accumulating data are present in the field of IBD (Crohn's Disease-CD and Ulcerative Colitis-UC), a close enteritis to campylobacteriosis. The metabolomics of IBD patients is shifted from healthy subjects with characterization of increased bile acids, taurine, and tryptophan [99]. Out of the 2,729 differentially abundant metabolites, the majority (71%) are significantly depleted in IBD relative to non-IBD controls; 8% are significantly elevated in both CD and UC; 19% are specifically elevated in CD; and only 3% are specifically elevated in UC [100]. Specifically, IBD enriches lactate, sphingolipids, and primary bile acids of cholate (CA) and chenodeoxycholate (CDCA) but with reduction of triterpenoids, pantothenate, long-chain fatty acids, phenylbenzodioxanes, cholesterols (including cholestenone), triacylglycerols (TAGs), and secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA). Interestingly, IBD patients show a decrease in obligately anaerobic producers of short-chain fatty acids [90].

Furthermore, IBD patients have increased polyunsaturated fatty acids (e.g., adrenate and arachidonate) but reduced pantothenate and nicotinate [101]. CD patients have increased levels of conjugated and sulfated bile acids in the feces [102]. In a functional analysis with shotgun metagenomics data, sulfur metabolism is identified with an enrichment of sulfonate, methionine, cysteine and taurine transport systems in mice colonized with microbiota from active IBD patients [88]. These metabolic changes are consistent with the increased abundance of sulfate-reducing bacteria (e.g., *Desulfovibrio*, *Clostridia, Bilophila*, and *Bacteroides fragilis*), some of which use sulfate as a terminal electron acceptor for respiration and concomitantly produce hydrogen disulfide, a toxic metabolic byproduct [88]. In accordance with IBD, secondary bile acid DCA, but not LCA and ursodeoxycholic acid, reduces *C. jejuni* counts and moderates intestinal microbiota composition in broiler birds [79]. DCA also reduces *C. jejuni*-induced colitis in ex-germ free *Il10*$^{-/-}$ mice [85]. Together, microbiota metabolites play an essential role on enteritis such as campylobacteriosis and IBD, and finding additional metabolites will assist development of therapeutic agents.

One specific and well-studied bacteria-bacteria interaction through microbial metabolites is called quorum sensing (QS) [103]. When the number of bacteria in the surrounding environment reaches certain level, bacteria activate QS and release specific signaling molecules of autoinducers (AIs) to modulate the expression of themselves and surrounding others on virulence, the ability for invasion and colonization, and the formation of biofilm [104]. Two types of AIs have been studied. AI-1 is produced by N-acyl-homoserine lactones (AHL) synthase and mediates intraspecies communication in Gram-negative bacteria. AI-2 is produced by S-ribosylhomocysteine lyase (LuxS) and mediates both intra- and interspecies communication in Gram-positive or Gram-negative bacteria [103, 104]. LuxS/AI-2 system plays important roles in cell–cell interactions in *C. jejuni* [105, 106]. Because biofilm is crucial for *C. jejuni* survive outside of hosts and facilitates its transmission from chicken reservoirs to humans, LuxS-mutant strains show deficient in biofilm formation and possible reduction of their transmission [107]. *C. jejuni* 81176 luxS mutant shows significant decreased colonization in chickens [108]. Deletion of luxS gene in *C. jejuni* NCTC IA3902 strain completely inactivates its colonization in the

intestinal of chickens [109] or guinea pig [110], while the complemented strain with luxS gene restores the colonization ability comparable to the wildtype. It remains largely elusive what is the role of QS in the interaction of microbiota and *C. jejuni* and on the pathogen infectious capacity of colonization and induction of intestinal inflammation.

4. Microbiome-modulated immunity and campylobacteriosis

Because of their proximity, microbiome and gut immune system are actively interact with each other against the foreign substances and pathogens [11]. Gut microorganisms form a microbial community co-existed with the gut-associated lymphoid tissue [111], which is the largest immune organ in our body. Under normal circumstances, the intestinal epithelium and resident flora are separated by mucus layer, which not only provides static shielding, but also limits normal microbiomes' immunogenicity by imprinting dendritic cells [112, 113] that have ability to distinguish antigens present by normal microbiota and invaded pathogens [114]. Thus, the normal flora can live along with the host without causing damage, or getting removed by the host immunity [115]. The elimination of microbiomes results in a deficiency function of immunity, as a fact, antibiotics treated mice can be used as a model for the study of pathogen colonization [116]. Infectious pathogens often break gut microenvironment's equilibrium to generate ill effects, which may cause the gastrointestinal illnesses like campylobacteriosis. The normal flora have the capacity to induce lymphoid tissue's immune response to protect host from pathogens infection [117].

As one of the enteritis, campylobacteriosis has a common feature of leading extensive intestinal inflammation driven by Th1 and Th17 lymphocytes and TLR4 when homeostatic is perturbed [118], sharing typical pathology at cellular levels, such as neutrophils infiltration, leukocytes existence in fecal, and crypt abscesses. However, the pathogenesis of campylobacteriosis is not well studied. *C. jejuni* is commensalism with chickens [111], but causes diseases in humans [119]. Increasing data show that microbiomes play a pivotal role in modulating host immunity against campylobacteriosis and other enteritis. Better understanding the complex interaction between gut microbiome, pathogen *C. jejuni*, and host immune response is crucial for discovering new therapies to prevent and treat campylobacteriosis.

4.1 Immunity, microbiota, and *C. jejuni* interaction

The gut homeostasis is dependent on the symbiotic relationship interacts between microbiota and immunity, with the occasional breaks by intestinal diseases such as IBD and campylobacteriosis (**Figure 3**). Signals derived from gut microbiota are essential for the development of the immune system. Germ-free mice display impaired immunity maturation such as defective Peyer's patches (PPs), plasma cells, intraepithelial lymphocytes (IELs), antimicrobial peptide, IgA secretion, epithelial barrier function, and CD4+ T cell maturation [120–122]. Comparably, manipulating microbiota by antibiotic treatment or microbiota reconstitution (fecal microbiota transplantation, FMT) shows the essential role of the microbiota in immune homeostasis. FMT reduces dextran sulfate sodium (DSS)-induced mouse colitis with reduced $CD4^+$ T, $CD8^+$ T cells expressing, CD107a, MHC II-expressing, professional antigen present cells (APCs) expressing, while innate lymphocytes ILC2 and ILC3 are increased [123]. Human FMT to mice fails to resist *Salmonella* infection and restore the low levels of $CD4^+$ and $CD8^+$ T cells, proliferating T cells, dendritic cells, and antimicrobial peptide expression compared to mouse FMT

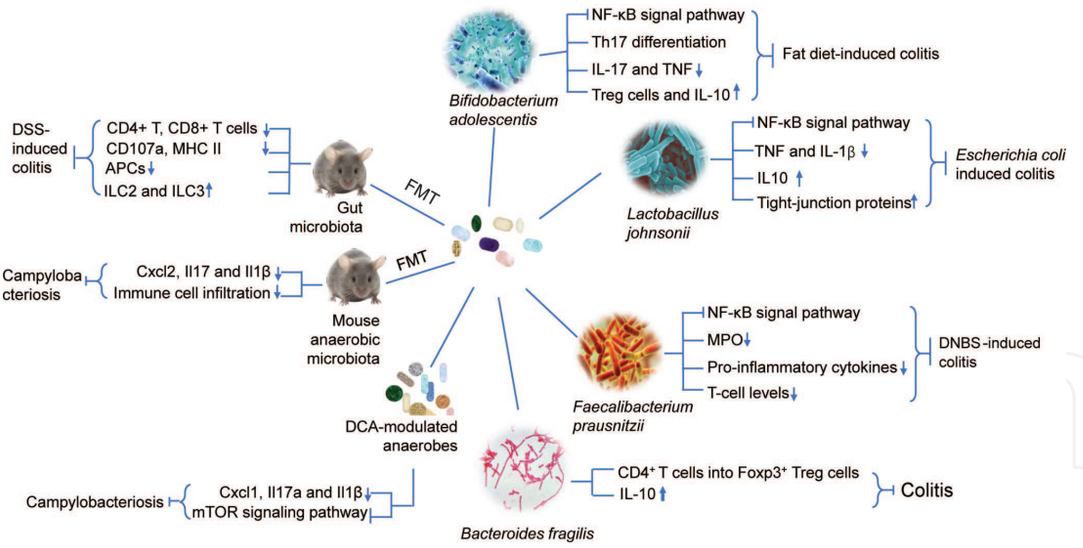

Figure 3.
Schematic illustration of the interaction of microbiota and immunity in campylobacteriosis.

[124], suggesting that gut immune maturation is dependent on colonization with a host-specific microbiota. Fecal Microbiota Transplantation (FMT) is successfully conducted on *Clostridium difficile* infection (CDI) patients by providing them with microbiomes from healthy donors to rebuilt the gut immunity [125] by inhibiting the activity of T cells and Th1 differentiation, preventing leukocyte adhesion, and production of inflammatory factors [126]. Consistently, ILC2-secreted IL-33 is essential for eosinophilia and tissue repair and survival, and its secretion is dependent on microbiota and can be rescued with FMT therapy to reduce *Clostridium difficile* infection (CDI) [127]. FMT of mouse anaerobic microbiota to germ free *Il10*$^{-/-}$ mice prevents *C. jejuni*-induced intestinal inflammation with reduced inflammatory genes of *Cxcl2*, *Il17* and *Il1β* as well as massive immune cell infiltration into gut lamina propria [85]. DCA-modulated anaerobes could attenuate chicken transmission exacerbated campylobacteriosis in mice by reduction of inflammatory genes, *Il17a*, *Il1β*, and *Cxcl1* expression in cellular level and inhibiting mTOR signaling pathway [128].

Beside microbiota transplantation, individual or groups of probiotics have been studied to reduce enteric pathogens, such as *Lactobacillus helveticus* [129], *Lactobacillus rhamnosus* LGG [130], *Lactobacillus gasseri* SBT2055 [131], *Lactobacillus* strains N8, N9, ZL4 and ZL5 [132], *Bifidobacterium longum* infantis [133]. *Lactobacillus* enhances macrophage elimination of *C. jejuni in vitro* and increases the expression of *Il1β*, *Il12p40*, *Il10*, and *Cxcl2* and the co-stimulatory molecules CD40, CD80, and CD86 [134]. Oral gavage of *Lactobacillus johnsonii* CJLJ103 inhibits LPS-induced NF-κB activation and *Tnfα* and *Il1β* expression, while expression of IL-10 and tight-junction proteins was increased [135]. *Lactobacillus plantarum* LC27 and *Bifidobacterium longum LC67* inhibits LPS, or 2,4,6-trinitrobenzesulfonic acid (TNBS)-induced colitis by suppress of NF-κB activation, CXCL4 expression and restored Th17/Treg balance [136]. Studies have shown that filamentous bacilli closely adhered to intestinal epithelium can induce Th17 reaction and increase the number of the anti-inflammatory Treg cells in the colon, and single colonization of *Bacillus fragilis* possesses immunomodulatory molecule-polysaccharide A (PSA), facilitates IL-10 producing through the conversion of CD4$^+$ T cells into Foxp3$^+$ Treg cells [137], and plays an important role in preventing and treatment of colitis in animals [138]. *Faecalibacterium prausnitzii* was reduced in patients with Crohn's disease [139]. *F. prausnitzii* supplementation prevents dinitrobenzene sulfonic acid (DNBS)-induced mouse colitis with inactivation of NF-κB signal

pathway, down-regulation of MPO, pro-inflammatory cytokines, and T-cell levels [140]. With the advanced research on microbiota and immunity, it is expected that individual bacteria or groups of bacteria will be used to control *C. jeuni* infection in the near future.

4.2 Immunity, microbial metabolite, and *C. jejuni* interaction

In addition to the direct talk between microbiota and gut immunity, microbiota metabolites influence intestinal immune homeostasis, which is dependent on the balance of pro- and anti-inflammatory response (**Figure 4**). As discussed in section 2.2, Treg is the key ant-inflammatory T cell with its signature cytokine IL-10. IBD patients show reduced SCFAs in stool compared to healthy people, a consistent observation with reduced butyrate-producing bacterial taxa [141]. SCFAs, such as butyrate, acetate, and propionate, are microbial fermentation products of polysaccharides [142]. SCFAs are the energy source for colonocytes that lining the gastrointestinal tract [143], which have antiproliferative and anti-inflammatory features [144, 145]. SCFAs promotes the differentiation of Treg cells and their anti-inflammatory IL-10 secretion [146]. Butyrate or mixtures of SCFAs in enemas show clinical and histological improvement in active UC patients and diversion colitis [147, 148]. At the molecular level, butyrate in enemas decrease NF-κB activation in macrophages from distal colon tissue of UC patients [149], and reduce LPS-induced cytokine expression, NF-κB activation in lamina propria, and the number of peripheral blood monocytes in CD patients [150]. *C. jejuni* expresses the highest levels of the SCFA-related genes (*ggt*, *peb1c*, and *Cjj0683*) and colonizes efficiently in SCFAs-rich chicken ceca compared to other intestinal segments [151]. It remains elusive what is the role of SCFAs on *C. jejuni*-induced campylobacteriosis.

Besides microbiota metabolites regulation immune cells, they also modulate immune signaling pathways. Caffeic acid (CaA) is a hydrolyzed metabolite of chlorogenic acid by gut microbial esterase. CaA reduces DSS-induced in C57BL/6 mice colitis through blocking NF-κB signaling pathway, suppressing the secretion of IL-6, TNFα, and IFNγ, and inhibiting the infiltration of $CD3^+$ T cells, $CD177^+$ neutrophils and $F4/80^+$ macrophages [152]. L-arabinose, the digestion production of fiber, inhibits DSS-induced colitis by downregulating p38−/p65-dependent inflammation activation [153]. β-glucan is a polysaccharide naturally appeared in the cell walls of cereals, bacteria, and fungi. β-glucan reduces DSS-induced IBD by downregulating pro-inflammatory cytokines (TNFα, IL-6 and IL-8) and

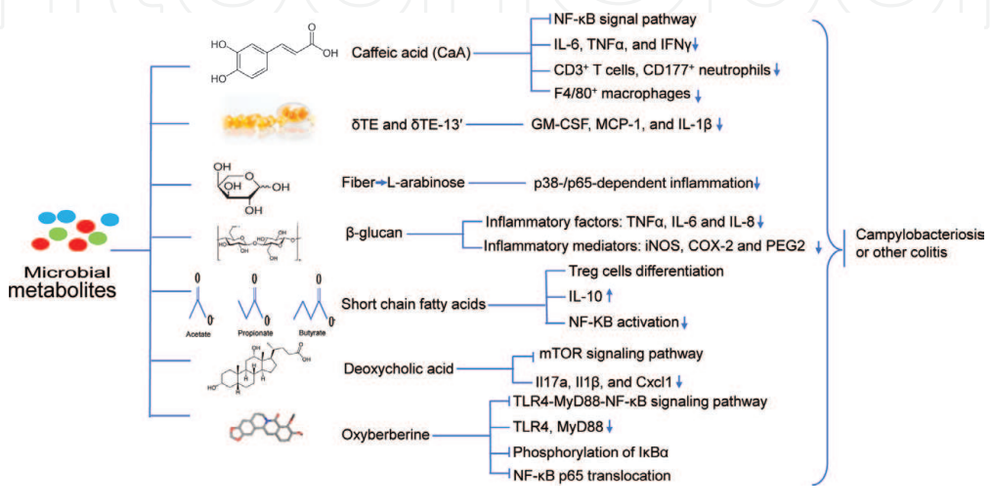

Figure 4.
Schematic illustration of the role of microbiota metabolites and immunity in campylobacteriosis.

inflammatory mediators (iNOS, COX-2 and PEG2) [154]. Oxyberberine, a gut microbiota metabolite of berberine, shown anti-colitis effect through the inhibition of TLR4-MyD88-NF-κB signaling pathway with reducing phosphorylation of IκBα and translocation of NF-κB p65 from cytoplasm to nucleus [155]. Notably, microbiota metabolic product DCA reduces *C. jejuni*-induced intestinal inflammation in *Il10*$^{-/-}$ mice with reduced inflammatory genes of *Cxcl2*, *Il17* and *Il1β* as well as massive immune cell infiltration into gut lamina propria [85]. Increasing microbiota metabolites will be discovered to attenuate *C. jejuni*-induced campylobacteriosis.

Furthermore, microbiota mediated metabolites are the important nutrients for host growth and immunity. Germ-free mice are usually more susceptible to infection diseases and show deficient to Vitamin K and B6 [156, 157]. Gut microbiota-synthesized Vitamins B12 and folate are vital for red blood cells synthesis, and red blood cells are crucial for supplying oxygen to immune cells and participating in the defensive process against pathogens [158]. Vitamin E delta-tocotrienol and its metabolite 13′-carboxychromanol inhibit tumor-associated colitis by reduction of pro-inflammatory cytokines GM-CSF, MCP-1, and IL-1β, respectively [159].

5. Conclusion

Given the fast research advancement on mucosal immunology, microbiota, and metabolomics recently in gastroenterology field, it is better than ever to investigate the mechanism of immunity-microbiota interaction and to use the knowledge to prevent and treat campylobacteriosis. The gut adaptive and innate system is the key for the permission or resistance to enteric pathogens and their induction of intestinal inflammation. Microbiota and its metabolic products or metabolites are essential for preventing gut pathogen invasion and the enteritis. Together, the development and function of the intestinal immunity is modulated by intestinal microbiota and its metabolic activities and products. Indeed, microbiota reconstitution by FMT is able to prevent or treat a number of intestinal disorders such as human CDI and mouse campylobacteriosis. Consistently, supplementing microbial metabolite of secondary bile acid DCA prevents campylobacteriosis in mice. Based on the successful or failed examples of the microbiome intervention on intestinal diseases, it is reasonable to conclude that a better knowledge on disease etiology and microbiome status during health and the diseases are essential for specifically targeting the pathogenic driving factors to prevent and treat the enteritis. Additional research will open new avenues to elucidate the in-depth understanding of the role of immunity and microbiota and to develop therapeutic approaches to control enteritis such as campylobacteriosis.

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Conflict of interest

The authors declare no conflict of interest.

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