Molecular Pathology of Campylobacter

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ABSTRACT

Campylobacter spp. are globally prevalent zoonotic pathogens causing bacterial diarrheal diseases. Found in warm-blooded animals and diverse environments, they transmit to humans through contaminated water, food, or contact with diseased animals. Human campylobacteriosis, caused primarily by Campylobacter coli (C. coli) and Campylobacter jejuni (C. jejuni), manifests as gastroenteritis and ranks among the leading causes of global diarrheal diseases. These infections can lead to severe complications, including autoimmune disorders like Guillain-Barre syndrome (GBS). In animals, infections can result in clinical effects like abortions, liver disease, and infertility. Campylobacter spp. lack typical human disease virulence factors, suggesting that clinical symptoms in campylobacteriosis are primarily triggered by the host immune response. This chapter explores the intricate interactions between C. jejuni and host tissues, focusing on the molecular pathology and inflammatory responses elicited, with an emphasis on the involvement of immune cells. The gastrointestinal epithelial cells play a crucial role in the initial stage of responding to C. jejuni infections through adhesion and extracellular sensing. Toll-like receptors (TLRs) are involved in detecting invasive infections, triggering proinflammatory responses. Upon invasion, C. jejuni uses Campylobacter invasion antigens (Cia) to penetrate intestinal cells, leading to increased IL-8 secretion and neutrophil chemotaxis. The genotoxin cytolethal distending toxin (CDT) and CRISPR-associated gene 9 (CjeCas9) contribute to host DNA disruption, apoptosis, and inflammation. Neutrophils, eosinophils, and mast cells play roles in tissue damage, with neutrophils restricting C. jejuni growth and eosinophils exhibiting activation responses. The adaptive immune response involves B and T lymphocytes generating antibodies and cytotoxic T cells respectively. Monocytes/macrophages, dendritic cells, and natural killer (NK) cells act as key players bridging innate and adaptive immunity, with various roles in inflammation, tissue repair, and modulating immune responses. NK cells interact with C. jejuni components to suppress inflammation and coordinate T lymphocyte responses. Understanding these complex interactions is crucial for unraveling the mechanisms underpinning Campylobacter-induced tissue pathology and inflammation, paving the way for advancements in disease management and prevention.

Keywords: Campylobacter jejuni (C. jejuni), Gastroenteritis, Immune response, Neutrophil extracellular traps (NETs), Macrophages, Inflammation

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1. INTRODUCTION

Campylobacter spp. are important zoonotic pathogens and are one of the most prevalent causes of bacterial diarrheal diseases around the globe (Olvera-Ramírez et al. 2023). *Campylobacter* spp. inhabits a wide variety of environments, and the *Campylobacter* genus is frequently found in the intestine of warm-blooded animals, such as ruminants, poultry, and pigs. Its transmission to humans can occur by consuming tainted water or food or by coming into close contact with diseased animals (Chlebicz and Śliżewska 2018; Bunduruș et al. 2023). Wildlife can also have high pathogen-shedding potential and may play a crucial role in the spread of these zoonotic pathogens (Olvera-Ramírez et al. 2023). Even though there is a modest danger of zoonotic agents in wild birds infecting humans, this issue is thought to be a developing concern (Wei et al. 2019). The *Campylobacter* genus species have been classified using studies based on their prevalence in a range of animals and environmental reservoirs (Soto-Beltrán et al. 2023). The infection brought on by members of the genus *Campylobacter* in humans is known as human campylobacteriosis. Human campylobacteriosis exhibits gastroenteritis and is among the four main causes of diarrheal diseases around the globe (WHO 2020). Although the primary causes of human campylobacteriosis are *Campylobacter coli* (*C. coli*) and *Campylobacter jejuni* (*C. jejuni*) (Man, 2011) but a wide range of other *Campylobacter* species such as *Campylobacter fetus* (*C. fetus*), *Campylobacter mucosalis* (C. *mucosalis), Campylobacter concisus* (*C. concisus*), *Campylobacter upsaliensis* (C. *upsaliensis*), *Campylobacter rectus* (C. *rectus*), and *Campylobacter lari* (C. *lari*) have also been recovered from human clinical samples (Sheppard et al. 2009; Igwaran and Okoh 2019).

Abdominal pain, diarrhea, malaise, and fever are clinical outcomes of *Campylobacter* infections. Even though symptoms are typically self-limiting and may last for up to two weeks, the illness can occasionally be more severe and can have post-infection sequelae (Tegtmeyer et al. 2021). Certain other gastrointestinal conditions, like esophageal diseases, inflammatory bowel disease, colon cancer, cholecystitis, celiac disease, and periodontitis, can also be caused by *Campylobacter* species (Verdu et al. 2007; Kaakoush et al. 2015). The *Campylobacter* infections can be followed by fatal, life-threating autoimmune disorders such as Guillain-Barre syndrome (GBS), reactive arthritis (ReA), Miller Fisher syndrome, and irritable bowel syndrome (IBS) (Callahan et al. 2021; Soto-Beltrán et al. 2023). *C. concisus*, a member of the other emerging group of *Campylobacter*s spp. that are typical in human oral commensal flora, has lately been associated with non-oral conditions (Kato et al. 2023). Campylobacteriosis can develop at doses as minimal as 800 colony-forming units (CFU), while *C. jejuni* infections can develop at doses as minimal as 360 CFU (Hara-Kudo and Takatori 2011).

In 1909, *Campylobacter* spp. was first recognized as a source of animal disease, yet until 1980, it was not identified as a cause of infection in humans (Galate and Bangde 2015). *Campylobacter* species are frequently cited as a prominent source of bacterial gastroenteritis in both developed and developing nations (EFSA 2021). The *Campylobacter* genus belongs to the family *Campylobacteraceae*, the order *Campylobacterales*, and the class *Epsilonproteobacteria* (Vandamme et al. 2015). The *Campylobacter* genus currently has 32 officially recognized species, along with 9 subspecies and 4 biovars (ITIS 2020). *Campylobacters* are Gram-negative, microaerophilic, corkscrew-shaped bacteria with a size range of 0.5 to 5 µm in length and 0.2 to 0.9 microns in width (Wassenaar and Newell 2006; Vandamme et al. 2015). Majority of the *Campylobacter* species are fastidious organisms that often demand a microaerophilic environment for growth (Soto-Beltrán et al. 2023). The ideal temperature for the growth of

thermotolerant *Campylobacter* species is between 37 and 42°C, and the thermotolerant *Campylobacter* species include *C. coli, Campylobacter insulaenigrae* (*C. insulaenigrae*), *C. upsaliensis, Campylobacter helveticus* (*C. helveticus*), *C. lari,* and *C. jejuni* (Wassenaar and Newell 2006; Vandamme et al. 2015). While other *Campylobacter* species except of these thermotolerant *Campylobacter* are thought to be non-thermotolerant, having an optimum temperature of growth, i.e., 37°C (Soto-Beltrán et al. 2023). The environmental abundance of thermophilic *Campylobacter* species eventually acts as a bridge for the spread of this bacterial pathogen between various hosts and habitats (Dearlove et al. 2016; Gölz et al. 2018).

Complex gastroenteritis may develop as a result of the *Campylobacter* bacterium's unusual capacity to adapt to various settings; in certain situations, this condition may be difficult to treat due to increased resistance to various medications (Bunduruş et al. 2023). The pathogenic *Campylobacter* spp. have the ability of long-term survival in food products, regardless of their inability to flourish outside the homeotherms' digestive tracts. These bacteria are typically vulnerable to environmental stress, yet they have evolved a variety of survival strategies for the environment and the food chain, which can result in human infections (Chlebicz and Śliżewska 2018). A wide range of virulence factors are encoded by the *Campylobacter* genome, giving the bacterium capacity to affect host immunological defenses, make biofilms, and withstand antimicrobials, which ultimately increase its infection-inducing potential (Bunduruş et al. 2023). *Campylobacter* spp. can contaminate both dairy products and meat; however raw milk is particularly prone to infection (Newell et al. 2017; Chlebicz and Śliżewska 2018). Chicken meat can get contaminated with *Campylobacter* at slaughterhouses due to *Campylobacter*-infected chickens' gut content coming into contact with chicken carcasses (Newell et al. 2011).

Campylobacter spp. infections can also occur in animals and can make them experience a range of clinical effects. For example, *C. fetus* subsp. fetus causes abortions in cattle, goats, and sheep; *C. hepaticus* induces spotty liver disease in layer hens; and *C. fetus* subsp. venerealis causes infertility in cattle (Courtice et al. 2018; Crawshaw 2019). *Campylobacter* colonization in chicks typically occurs at 2-3 weeks of age, but they are usually asymptomatic after colonization (Newell and Fearnley 2003; Awad et al. 2015; Connerton et al. 2018). In infected chickens, *Campylobacter* spp. colonizes the mucosa of the cloaca crypts and cecum, and chickens may also have these bacteria in their liver and spleen (Chlebicz and Śliżewska 2018). Wildlife can also serve as a reservoir, amplifying hosts, and even a source of *Campylobacter* (Becker et al. 2015). Particular emphasis has been placed on the origin of these strains, and it has been suggested that chicken's *C. hepaticus* could have an environmental origin (Phung et al. 2020; Wu et al. 2022).

Most of the investigations are centered around *C. jejuni*, as it is the most common cause of diarrheal illnesses even in the industrialized world. *Campylobacter* spp., in contrast to other bacteria that cause gastrointestinal tract diseases, lacks some of the traditional virulence factors that are frequently linked to cause disease in humans. Therefore, it is thought that the host immunological response to the bacteria is principally responsible for the clinical symptoms of human campylobacteriosis and the gastrointestinal disease. Since gastrointestinal disease is typically caused by the host's immunological response, the onset of postinfectious disorders may come from the misdirection or dysregulation of the same inflammatory response (Callahan et al. 2021). Therefore, it is crucial for human health and the disease diagnostic fields to understand the molecular pathology, mainly including the cellular immune responses to *Campylobacter* and the immunological events crucial for the disease onset and the post-infectious disorders (Callahan 2023).

Molecular pathology is a branch of the biomedical sciences that concentrates on the development, progression, and evolution of diseases on the molecular level. Molecular pathology is typically treated as a subgroup of the pathology. In traditional pathology, the morphological manifestations of disease are focused. However, molecular pathology also incorporates molecular biology tools in order to: isolate and identify the infectious disease-causing agents; comprehend differential gene expression role in disease etiology; provide more precise methods of disease diagnosis; and offer more individualized therapy options. Molecular pathology can be approached from a variety of perspectives, and it also incorporates

immunology, genetics, and other medical field aspects. Cell culture and cell isolation are the main approaches utilized in molecular pathology to determine links between gene alterations and disease. The other methods used in molecular pathology involve tissue microdissection methods, gel electrophoresis methods, amplification methods, hybridization methods, and nucleic acid sequencing. Nucleic acid sequencing further consists of proteomics, and DNA microarrays. Along with being used in biomedical research to understand specific disorders, molecular pathology also has practical applications for patients. The development of molecular diagnostics is a result of biological breakthroughs that have led to an improved understanding of the molecular mechanisms. Prior to this comprehension, morphologic observations were used for the diagnosis of different states of disease (Kaoud 2012).
An insight into *Campylobacter* host tissue pathology and inflammatory responses, along with the aspects of the host's immune cells involved, is given below.

2. EPITHELIAL CELLS

There are two processes that happen within epithelial cells. These are;

2.1. ADHESION AND EXTRACELLULAR SENSING

Gastrointestinal epithelial cells, along with acting as a physical barrier, are also fitted with intracellular and extracellular receptors that may, respectively, detect invasive infections and sample the lumen of the gut (Tang et al. 2016). *C. jejuni* can penetrate the distal intestine and proximal colon mucus layer to make it to the intestinal epithelial cells (IECs) apical surface after being ingested in fairly small infectious doses via contaminated drinking water or food (Chang and Miller 2006; Teunis et al. 2018). *C. jejuni* can attach to IECs and infiltrate them once it has passed through the mucus layer (Hendrixson and DiRita, 2004; Lugert et al. 2015). Toll-like receptor (TLR) reporter HeLa cells have been reported to be triggered by lysed *C. jejuni* via the sensing activities of different TLRs used to sense the bacterium. These TLRs include TLR1/2/6 and TLR4, which recognize bacterial lipoproteins and lipopolysaccharides, respectively. NF-κB is activated by these TLRs being stimulated, which is transduced via the MyD88 signaling cascade. IL-1β, IL-8, IL-12p42, GRO-α, tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein 1 (MCP-1) are all produced and secreted as a result of NF-κB activation (Konkel et al. 2020). TLR4 activation also activates the Toll/IL-1R domain-having adaptor-inducing IFN-β (TRIF) signaling cascade, culminating in IFN-β production (Hu and Hickey 2005; de Zoete et al. 2010; Yu and Gao 2015). Human IECs release IL-8 after being stimulated by *C. jejuni*, which then encourages chemoattraction along with numerous neutrophils recruitment to the infection site (Hickey et al. 2000). Along with IL-8, a proinflammatory cytokine called IL-6, required for mounting an adaptive immune response, is released when IEC TLR1/2/6 are stimulated (Friis et al. 2009). Beta-defensins 2 and 3 are also produced by IECs in response to *C. jejuni* stimulation, although the stimulus necessary for induction is yet undefined (Zilbauer et al. 2005). Beta-defensins are secreted cationic antimicrobial peptides that can attach to the bacterial membranes, which are negatively charged, prompting leukocyte chemoattraction and bacterial cell death (Cobo and Chadee 2013).

2.2. INVASION AND INTRACELLULAR RESPONSES

C. jejuni enters IECs once it has reached the apical surface, and this invasion is reliant on the *Campylobacter* invasion antigen (Cia) protein secretion (Buelow et al. 2011). Cia proteins, along with encouraging cellular invasion, can also activate the extracellular signal-regulated kinases (ERK) and p38 mitogen-activated protein (MAP) kinase pathway to increase IL-8 secretion from IECs. This increased IL-8 production from IECs causes robust neutrophil chemotaxis to the infection site. Eventually, *C. jejuni*

invades IECs by remodeling host microtubules and actin, even though it doesn't seem to create actin tails for intracellular trafficking. This indicates that *C. jejuni* continues to retain itself within a *Campylobacter*-containing vesicle (CCV) (Watson and Galán 2008; Samuelson et al. 2013). Some strains of *C. jejuni* produce cytolethal distending toxin (CDT), a genotoxin, once they are intracellular. CDT can induce cell cycle arrest, cell swelling, and cell distension (Lara-Tejero and Galán 2000; Scuron et al. 2016). Epithelial barrier disruption and impairment of signaling pathways, which change the immune response of the host, are predicted outcomes of this cellular response (Scuron et al. 2016). The formation of the CCV in IECs may be significantly influenced by CDT. Furthermore, the bacterium may use alternative strategies to target the DNA of the host, as *C. jejuni* strains without CDT nonetheless cause disease and DNA damage. For instance, it was recently shown that *C. jejuni*, while in IECs, explains clustered regularly interspaced palindromic repeat (CRISPR)-associated gene 9 (CjeCas9) linked with the outer membrane vesicle. The CjeCas9 gene can target the DNA of the host, causing epithelial cell death right after being released, along with the proinflammatory gene expression's upregulation (Saha et al. 2020; Saha et al. 2020). Furthermore, several investigations have shown that *C. jejuni* triggers IECs' caspase-3-dependent apoptosis, although the behind mechanism of this reaction is yet undefined (Butkevych et al. 2020). Since it seems that *C. jejuni* uses a variety of mechanisms to disrupt the DNA of the host and those responses could induce inflammation. Therefore, more studies should be done to fully characterize these systems and understand how they affect tissue pathology and inflammation (Callahan et al. 2021).

IECs have the ability to sense intracellular *C. jejuni* along with responding to extracellular bacteria. Intracellular *C. jejuni* can activate TLR9, which further recognizes intracellular DNA (de Zoete et al. 2010). Furthermore, nucleotide-binding oligomerization protein (NOD) receptors seem to be involved in the recognition of intracellular *C. jejuni.* The lack of NOD2 in colonocytes may inhibit the host immunological response, leading to an increase in the bacterial burden; however, other immune cells, such as macrophages and dendritic cells (DCs), express NOD2 (Moreira and Zamboni 2012). In fact, NOD2 activates the antibacterial function in IECs, particularly against *C. jejuni* (Barnich et al. 2005). Additionally, in response to *C. jejuni*, NOD1 is also activated, which causes a decrease in intracellular *C. jejuni* and an increase in hBD2 and IL-8 (Zilbauer et al. 2007). Since NOD activation and cytotoxicity are closely related, it is possible to hypothesize that epithelial NOD signaling causes tissue pathology in infected people (Heim et al. 2019). This bacterium can travel to the colonocyte's basolateral side while inside the CCV and exocytose to the colon's underlying tissue to come into contact with chemoattracted leukocytes (Kopecko et al. 2001; Callahan 2023). It has been found that tight junction disruption brought on by *C. jejuni* causes barrier dysfunction, which in turn signals the production of pro-inflammatory cytokines. Proinflammatory cytokines include IL-1β, IL-6, IL-13, TNF-α, IFN-γ, and MCP-1 (Schmidt et al. 2019). Further research is required to determine how this virulence factor affects inflammation during campylobacteriosis because tight junction proteins are crucial for controlling intestinal inflammation following damage (Slifer and Blikslager 2020).

Neutrophils, eosinophils, and mast cells are also involved in *Campylobacter*-induced tissue damage and pathology, along with generating innate immune cell responses (Callahan et al. 2021).

3. NEUTROPHILS

Neutrophils are the first innate immune cells drawn to the infection site after *Campylobacter* effectively penetrates the epithelial barrier (Kolaczkowska and Kubes 2013). The three primary antibacterial functions of neutrophils include microbe degradation, phagocytosis, antimicrobial proteins release via degranulation, and the exclusion of neutrophil extracellular traps (NETs) (Callahan et al. 2021). Due to their high proinflammatory activity and abundance in colonic tissue during *C. jejuni* infection, neutrophils must be taken into account as a possible cause for acute and chronic illnesses as well as tissue pathology.

Neutrophils move from the basolateral to the apical side of the epithelium within colonic crypts, which are reliant on 12-lipoxygenase (12-LOX), a host-derived enzyme, and n-formyl peptides from bacterial sources (Murphy et al. 2011). The interaction between *C. jejuni* and neutrophils causes complement-opsonized cells to be phagocytosed, leading to the generation of reactive oxygen species (ROS), which directly kills the bacterium and causes localized tissue damage (WALAN et al. 1992; Heimesaat et al. 2023). Along with phagocytosis and direct cell death, a large number of neutrophil-derived antimicrobial proteins are released into the surrounding tissue, and they build up in the feces of individuals with a *C. jejuni* infection. These antimicrobial proteins include neutrophil elastase (Ela2), lipocalin-2 (Lcn2), calgranulin C (S100A12), and myeloperoxidase (MPO). These antimicrobial proteins' activities indicate that during an infection, their release is a possible factor in the growth restriction of *C. jejuni*, and these proteins are probably released as a consequence of degranulation. Ela2 and MPO were also observed to colocalize with NETs in the infection brought on by *C. jejui* (Shank et al. 2018; Callahan et al. 2020). It has been hypothesized that NETs play part in the intestinal pathology and formation of crypt abscess during campylobacteriosis because of their cytotoxic nature. These NETs may have a significant impact on the emergence of the postinfectious disorders outlined in the introduction, as these structures are linked to a variety of autoimmune diseases (Li et al. 2020). More investigation into *C. jejuni*-neutrophil interactions is required because of the link between pathology, inflammation, neutrophil activity, and the emergence of autoimmune diseases (Callahan 2023).

4. EOSINOPHILS

Eosinophils are effectively activated in vitro by *C. jejuni*, which causes degranulation, chemotaxis, a respiratory burst, and eosinophil cationic proteins (ECPs) release. Although, the involvement of eosinophils in campylobacteriosis has received scant direct evidence (Svensson and Wennerås 2005; Hogan et al. 2013). Despite the eosinophil's rarity, their response to *C. jejuni* and their function in gastrointestinal inflammation have led to hypothesis that they may play a role in the emergence of post-infectious disorders as well as in inflammation during infections (Callahan et al. 2021).

5. MAST CELLS

Mast cells are recognized as inflammatory granulocytes, and they release a number of cytokines and histamine (Krystel-Whittemore et al. 2016). It is thought that mast cells have a small role in infection, despite the fact that they have been identified in the stools of individuals infected with *Campylobacter* (Hendrixson and DiRita 2004). Mast cell closeness to enteric nerves was observed to be correlated with stomach pain during IBS, so even though mast cells do not seem to be directly implicated in campylobacteriosis, their participation in gastroenteritis cannot be completely dismissed (Callahan et al. 2021).

Both B and T lymphocytes are also engaged in *Campylobacter*-generated infection. B cell responses occur along with antibody production, while T cell responses occur alongside subtype switching. Both together constitute the adaptive immune response (Callahan et al. 2021; Al-Naenaeey et al. 2022).

6. B Lymphocytes

In order for humoral immune responses to begin, antigen-reactive B cells must be exposed to antigens. Titers of serum IgM, IgA, and IgG antibodies relevant to bacterial epitopes peak approximately 11 days following infection with *C. jejuni* in humans (Black et al. 1988). Autoreactive IgG1 antibodies are the most prevalent subtype of antibodies produced after campylobacteriosis (Malik et al. 2014). As there is a significant link between IgG1 levels and GBS severity, it has been proposed that this reaction is crucial to

the GBS development following infection with *C. jejuni*. On average, GBS can affect 1/900 people. This proposition is largely supported by the finding that a number of the IgG and IgA antibodies generated during infection may also cross-react with the human GM1 gangliosides found in the neurons (Masanta et al. 2013). Also, this reaction is probably brought on by some LOS core oligosaccharides of *C. jejuni* that mimic human ganglioside GM1 structures (Yuki et al. 2004). However, to comprehend the biochemical, genetic, and molecular underpinnings of these responses, additional research must be undertaken (Callahan et al. 2021).

7. T Lymphocytes

Studies have shown that there is likely a connection between tissue pathology and inflammatory T lymphocyte activities (Malik et al. 2014). IL-12, which is secreted by mature dendritic cells during the later stages of infection, encourages naive T cells to develop into T helper 1 (Th1) cells, which then generate IFN-γ (Hu et al. 2006; Rathinam et al. 2009). Th1-derived cytokines, once they had undergone differentiation into Th1 lymphocytes, peak 7 to 14 days after infection, with IFN-γ^+ $CD4^+$ T cells being the most prevalent lymphocyte in humans infected with *C. jejuni* (Fimlaid et al. 2014). These findings lead to the hypothesis that campylobacteriosis is predominantly a Th1 lymphocyte illness with a secondary development of Th17 cells. Patients may have a higher proportion of Vδ1 γδ (Vδ 1) $CD8^+$ T cells among the T cells generated during human *Campylobacter* infection, which is particularly intriguing given that these cells are linked to autoimmunity and cytotoxicity (Scelsa et al. 2004; Presti et al. 2021). Proinflammatory cytokines can activate the Vδ 1 T cell receptor (TCR) in the colon and intestines, and DCs can also activate Vδ 1 cells by utilizing microbial antigens, particularly lipid extracts from Gram-ve bacteria. The effective immunoregulation and host defense linked to Vδ 1 T cells depend on this recognition (Das et al. 2004). TLR4, an antigen linked to the previously described GM1 ganglioside, may also help T lymphocytes identify *C. jejuni* LOS (Cutillo et al. 2020). T cells may therefore be extremely important in the tissue pathology and the emergence of autoantibodies subsequent to campylobacteriosis (Callahan et al. 2021). Fig. 1 shows the body cells evoked in response to *Campylobacter* infection. Monocytes/macrophages, natural killer cells (NK cells), and dendritic cells are also produced in response to infection brought on by *Campylobacter*. These cells bridge the gap between the innate and adaptive immune responses (Callahan et al. 2021; Callahan 2023).

8. MONOCYTES/MACROPHAGES

Monocytes play a role in pathogen identification and inflammation, and monocyte-derived tissue-resident memory macrophages perform essential immunological tasks. These immunological tasks include anti-inflammatory signaling pathway promotion and tissue repair (Ginhoux and Jung 2014). Tissue-resident macrophages particularly ingest and degrade foreign material, debris, and dead cells, along with performing the functions of coordinators of the tissue's inflammatory immune response and expert antigen presenters (Varol et al. 2015). The human peripheral blood mononuclear cells (PBMC) were discovered to release an increased amount of IL-6 and IL-8 in the wake of infection (Hamza et al. 2017). By utilizing macrophage-like differentiated THP-1 cells, IL-8 secretion was also observed, demonstrating the importance of neutrophil chemotaxis during infection (Jones et al. 2003). Differentiated macrophages are effective at eliminating intracellular bacteria because *C. jejuni* is unable to evade being delivered to lysosomes; however, some strains of the bacterium can survive intracellularly inside monocytes and can cause apoptosis (Hickey et al. 2005). More investigation is required to comprehend the molecular mechanisms behind the proinflammatory switches that occur in macrophages and monocytes infected with *C. jejuni* (Callahan et al. 2021).

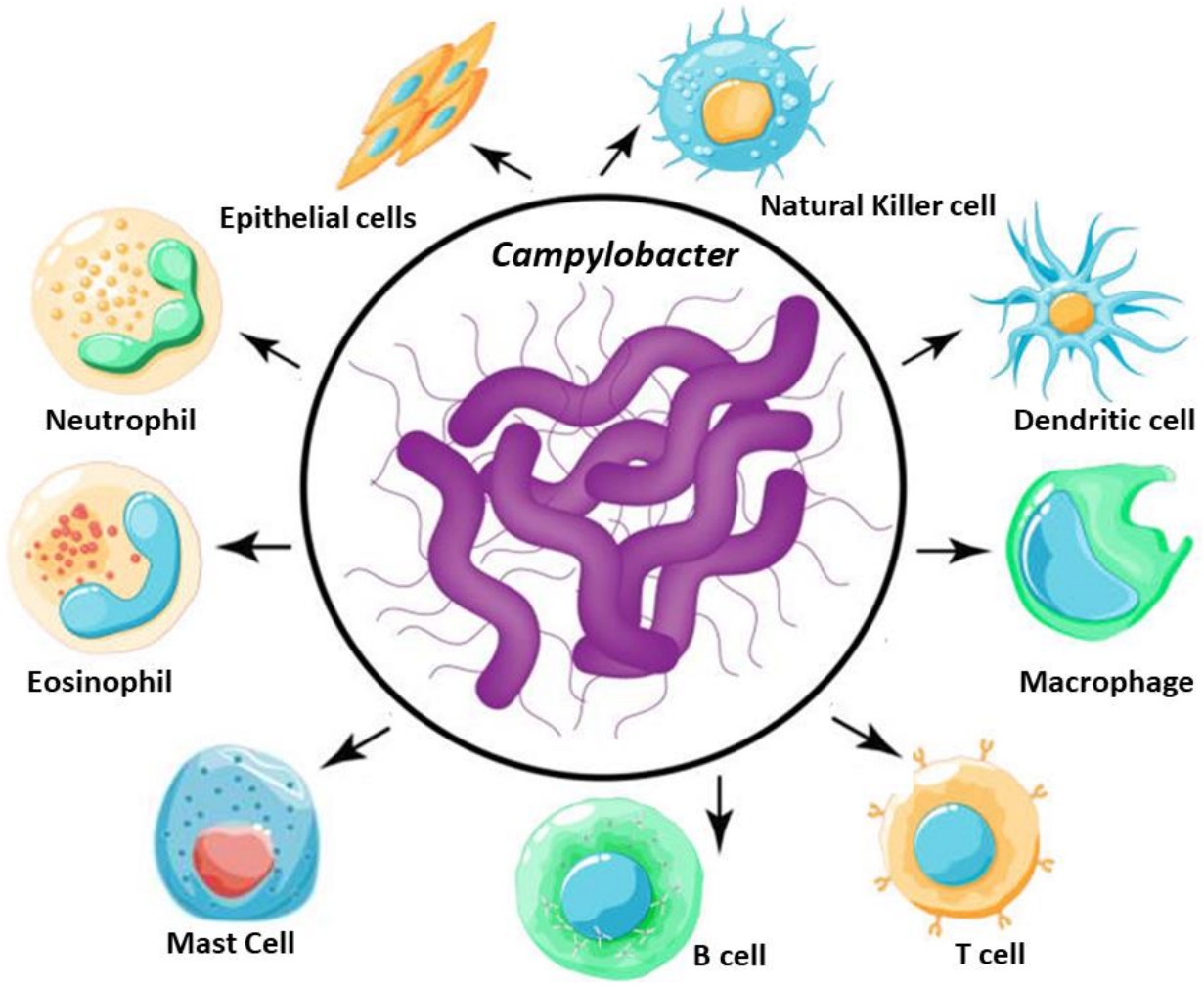

Fig. 1: Major body cells engaged in *Campylobacter*-induced infection

9. DENDRITIC CELLS

Dendritic cells (DCs), which serve as professional antigen-presenting cells activating the adaptive immune response, can also originate from monocytes (Patente et al. 2019). As DCs sample the intestinal lumen and transcytose during infection, they most likely come into contact with *Campylobacter* in the lamina propria intraluminally (Niess et al. 2005). Siglec-10-expressing DCs may contribute to *C. jejuni* mucosal immunity by acting as anti-inflammatory cells, in contrast to the crucial function that IL-10 plays in reducing intestinal inflammation. However, it has not yet been determined how these cells contribute to campylobacteriosis (Stephenson et al. 2014). Additionally, DCs triggered by *C. jejuni* release NF-κB-dependent chemokines, which further include growth-related oncogene α (GRO-α), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, monokine induced by gamma interferon (MIG), RANTES, and IP-10 (Hu et al. 2012). *C. jejuni* causes the phosphorylation of stress-activated protein kinase/Jun N-terminal protein kinase (SAPK/JNK), mitogen-activated protein kinases (MAPKs), P44/42, and P38 to induce chemokines and cytokines secretion. CD40, CD80, CD86, and mature phenotype cell surface major histocompatibility complex class II (MHC-II) are significantly upregulated after DCs are activated. DCs then

effectively internalize and eliminate *C. jejuni* (Hu et al. 2006). While campylobacteriosis appears to have anti-inflammatory effects from DCs, proinflammatory DCs in response to pathogen-associated molecular patterns within injured colonic tissue have also been shown in an increased amount (Stagg 2018). Therefore, it can be concluded that DCs are critical for campylobacteriosis, shaping and laying the groundwork for post-infection activity via the release of both anti-inflammatory and inflammatory cytokines, as well as antigen presentation (Hu et al. 2006; Callahan et al. 2021).

10. NK CELLS

NK cells react with the antigens of commensal and pathogenic bacteria, as well as with other various host cell types within the stroma and epithelium (Poggi et al. 2019). Siglec-7 molecules are used by NK cells to attach to the *C. jejuni* LOS, which promotes host inflammatory response and immunity (Avril et al. 2006). NK cells' cytotoxicity and activation pathways are diminished by Siglec-7, which ultimately reduces inflammation (Daly et al. 2019). The killer cell immunoglobulin-like receptor KIR2DS4 gets highly bound by conserved *C. jejuni* RecA epitopes provided by HLA-C*05:01 alongside LOS binding, which ultimately stimulates KIR2DS41 NK cells (Sim et al. 2019). Together, the aforementioned responses show that in the wake of *C. jejuni* infection, NK cells suppress the immune system for the host's advantage and coordinate T lymphocyte responses by antigen presentation (Callahan et al. 2021).

11. CONCLUSION

Campylobacter is the most common bacterium that causes gastroenteritis in people, although little is known about its host molecular pathology. Even though *C. jejuni* lacks the classical virulence factors that more thoroughly researched gastrointestinal pathogens have, it still invades the human GIT system and triggers a strong immunological response that seems to be the cause of significant immunopathology at the extraintestinal sites and colon. There is a significant knowledge gap in the host's molecular pathology in response to the infection brought on by *C. jejuni*, as it colonizes several mammals with a variety of clinical signs. Although this factor can help us understand each host's response to *Campylobacter* and it might also give an understanding of the divergent or shared evolution of immune mechanisms among various hosts. Therefore, the field of *C. jejuni* is an excellent spot to start comprehending the bacterial and host components that cause both systemic and colonic inflammation, along with the treatments and methods that might be useful for minimizing these effects. For instance, the current finding of innate memory may shed light on the autoimmunity that characterizes the postinfectious disorders of *Campylobacter* infections. The field of molecular pathology has made such great strides in recent times that these impacts can be comprehended in both in vivo and in vitro settings. By enhancing our knowledge of molecular pathology during and after infection, this discipline can commence devising strategies that might enable better understanding, diagnostics, and treatment of the disease, which will ultimately help to decrease *Campylobacter* prevalence across the globe.

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