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MINIREVIEW

Intestinal Immune Response to Human *Cryptosporidium* sp. Infection▽

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Cryptosporidium is an obligate intracellular protozoan parasite that is a major cause of diarrheal illness worldwide. *Cryptosporidium* primarily infects the distal small intestine. Immunocompetent hosts control and eliminate the infection, which typically causes acute, self-limited watery diarrhea lasting 5 to 10 days. However, in patients with defects in cellular immune responses (e.g., AIDS, malnutrition, or defects in the CD40-CD154 system), *Cryptosporidium* frequently causes persistent or chronic diarrhea and may also involve the biliary tract (40). In malnourished children, persistent diarrhea is associated with increased susceptibility to recurrent diarrheal episodes, which can lead to death or chronic nutritional and cognitive sequelae (1, 9, 33). Thus, the host immune response plays a critical role in the control of human cryptosporidiosis.

Although extensive studies with various animal models have provided important insight into the host immune response towards *Cryptosporidium parvum*, the ability of these models to explain the human immune response is limited. The clinical picture in rodents differs from that in humans, as mice do not get diarrhea after infection. Nonhuman primates, although probably the best in vivo model to mimic human disease, are difficult to work with, expensive, and not widely available. *Cryptosporidium hominis*, the pathogen causing most human cryptosporidiosis, infects only humans and gnotobiotic pigs, thus limiting data from animal models. Most importantly, comparison of animal and human data has shown that the immune response towards *Cryptosporidium* in humans differs significantly from that in animals; for example, in mice gamma interferon (IFN-γ) production seems to be associated with the innate and primary immune responses (35, 47), whereas in humans it is most probably associated with the memory response towards the parasite (93). Conducting studies to elucidate human mucosal immune responses is difficult. Patients with a natural infection would be the ideal subjects to study, but it is difficult to identify cases. Healthy human volunteers can be studied, but they typically experience a milder illness than malnourished children and AIDS patients. Human intestinal tissue samples can be obtained only by invasive procedures, limiting the numbers of subjects and samples available. Some data can be obtained from in vitro infections, but most of the target cells are immortalized and may not be ideal for studying mechanisms involving apoptosis. Furthermore, the immune cells in the peripheral blood may exhibit properties different from the properties of cells found in the intestinal compartment. Thus, knowledge about the human immune response towards *Cryptosporidium* infection is far from complete. Still, important recent advances have been made. The goal of this paper is to review the current literature to provide an understanding of the human immune response towards the parasite. We include some relevant data from other models only when the data shed light on studies performed with human cells or tissues.

LIFE CYCLE

Cryptosporidium has a complex life cycle, which takes place within the intestinal epithelial cell. Humans are infected after ingestion of the oocyst form. The infectious dose is low (less than 10 oocysts for some strains) (70). In the intestinal lumen, the oocyst releases sporozoites, which attach to host enterocytes and are enveloped. The parasites then enlarge and divide within the parasitophorous vacuole within the microvillus layer of the epithelial cell (21). After 48 to 72 h the host cell ruptures and releases the motile merozoites, which bind to the epithelial surface and reinvade. Some of the merozoites differentiate into sexual forms, which fuse to form the oocysts that are then shed into the intestinal lumen and the environment, where they can survive for many months before infecting a new host.

INTERACTION BETWEEN *CRYPTOSPORIDIUM* AND THE HOST EPITHELIAL CELL

Infection of the intestinal epithelial cells with *Cryptosporidium* activates an intracellular signaling cascade (Tables 1 and 2). In vitro infection of human cholangiocytes leads to upregulation of Toll-like receptors 2 and 4 and activation of the MyD88 pathway and other downstream molecules, finally

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TABLE 1. Cells and molecules involved in the human immune response directed against *Cryptosporidium* infection

Stage of infection	Molecules and cells activated or upregulated
Infection of epithelial cells	Toll-like receptors, MyD88, NF-κB, FAS/FAS ligand, caspase 3, Bcl-2, OPG, CXCL-8, CXCL-10
Innate response to primary infection	Natural killer cells, IL-15, CD40 ligand (CD154), TNF-α, IL-1β, prostaglandins, substance P
Immune response during repeated infection	$CD4^+$ T cells, IFN-γ
Anti-inflammatory response	IL-10, TGF-β

activating NF-κB (13). Whether the same parasite-host cell interactions occur in the intestinal mucosa in vivo is not known. Sporozoite invasion leads to complex effects on host epithelial cell apoptotic pathways in vitro. Invasion per se and early infection stimulate apoptotic pathways involving Fas ligand and caspase 3 (12, 62, 67). At the same time, activation of NF-κB upregulates antiapoptotic signals like Bcl-2 (11, 62, 67). The net effect on apoptosis in vitro varies at different time points after invasion. Between 6 and 24 h postinfection, antiapoptotic effects predominate (67). At 24 to 48 h postinfection, proapoptotic signals are more prominent (62, 67). This allows the parasite time to complete its life cycle (24 to 48 h) before the host cell dies and is shed.

TNF SUPERFAMILY RECEPTORS AND LIGANDS

In a recent study using microarray analysis of human intestinal explants, we noted that *Cryptosporidium* infection upregulates osteoprotegerin (OPG) mRNA in the host cell (8a). OPG is a molecule downstream of NF-κB and a member of the tumor necrosis factor (TNF) receptor superfamily, previously associated with bone metabolism (86). OPG lacks signaling mechanisms and functions as a decoy receptor. Its ligands include TNF-related apoptosis-inducing ligand (TRAIL), present on T cells and natural killer cells. We noted that TRAIL can cause apoptosis of infected cells. By binding TRAIL, OPG may prevent TRAIL-induced apoptosis. By evading early apoptosis, the parasite is able to grow and complete the intracellular part of its life cycle. Further studies should address other factors potentially involved in apoptotic signaling during early infection. CD40 ligand (CD154), another member of the TNF receptor superfamily expressed on the surface of activated T lymphocytes, is also important for the elimination of *Cryptosporidium*. Among others, the interaction of CD40 on antigen-presenting cells and CD154 on T cells provides a costimulatory signal that is important both for activating the T cells and for inducing antibody class switching from immunoglobulin M (IgM) to IgG, IgA, and IgE in B cells (32, 94). In humans, mutations in the CD154 gene lead to X-linked hyper-IgM syndrome, with secondary hypogammaglobulinemia and impaired T-lymphocyte function. The levels of serum IgA, IgE, and IgG are decreased (the level of IgM is normal or elevated), and T-cell proliferation upon antigen encounter and T-cell and macrophage effector functions are defective (94). Protracted or recurrent diarrhea and sclerosing cholangitis are common among patients with hyper-IgM syndrome. In these cases, *Cryptosporidium* is the most frequently identified pathogen (36, 53, 94).

TABLE 2. Factors whose function in parasite clearance requires further study

Compartment of immune response	Molecules and cells potentially activated or upregulated
Cellular immune response	Cytotoxic T cells (e.g., $CD8^+$ cells), TRAIL (cell bound and soluble)
Humoral immune response	B cells (serum and fecal IgA, IgM, and IgG)

CHEMOKINES

Activation of NF-κB leads to production and release of chemokines (43). Studies using human intestinal cell lines and xenographs demonstrated that there is increased expression of a range of chemokines after cryptosporidial infection (20, 50, 59, 83).

Studies of the chemokine CXCL-8 (also called interleukin-8 [IL-8]) in humans with cryptosporidiosis have yielded inconsistent results. CXCL-8 was expressed after in vitro infection of intestinal cell lines and human intestinal xenographs (50, 59, 83). Similarly, increased CXCL-8 levels were found in the stools of *Cryptosporidium*-infected Haitian children compared to controls (44, 45). Also, peripheral blood mononuclear cells (PBMC) of infected Haitian children expressed higher levels of CXCL-8 when they were restimulated in vitro up to 6 months after infection (45). In a study of Brazilian children, more stool samples containing elevated levels of IL-8 came from control children than from infected children (3). In analyzing intestinal tissues from AIDS patients with cryptosporidiosis, we did not detect CXCL-8 (90). Finally, CXCL-8 attracts mainly granulocytes. However, in studies of tissues from AIDS patients with cryptosporidiosis, granulocytes were not a prominent component of the inflammatory response except in patients coinfected with cytomegalovirus (26, 57). CCL5 (RANTES) was expressed by intestinal cell lines after *C. parvum* infection (20), but we observed that RANTES levels in intestinal tissues were not different in AIDS patients with cryptosporidiosis and uninfected controls (90). By contrast, the level of CXCL-10 (IFN-γ-inducible protein 10) was significantly elevated in the villus epithelial cells of AIDS patients with cryptosporidiosis (compared to AIDS patients without cryptosporidiosis or human immunodeficiency virus [HIV]-negative controls) (90). The higher the parasite burden, the more CXCL-10 was expressed. CXCL-10 functions to attract cells that carry its receptor, CXCR-3, which is normally expressed on lymphocyte subsets producing IFN-γ. Therefore, one possible interpretation of the upregulation of CXCL-10 is that in normal hosts CXCL-10 attracts effector cells, which in turn mediate parasite clearance (48, 90). In AIDS patients, the depletion of effector T cells may lead to increased numbers of parasites, causing exaggerated

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production of CXCL-10. Although potentially CXCR-3-positive cells localize to the epithelial layer, these cells are apparently unable to eliminate the parasite; instead, they may become targets for HIV infection. Successful antiretroviral therapy restores the number of $CD4^+$ T cells in intestinal tissues. We noted that *Cryptosporidium* clearance after successful antiretroviral therapy was associated with lower production of CXCL-10 by enterocytes (90). The decreased level of CXCL-10 might also reduce inflammatory responses in the intestinal mucosa and lead to amelioration of chronic diarrhea. In AIDS patients, the immune response during cryptosporidiosis may thus be both curative and part of the pathogenesis.

B CELLS AND ANTIBODIES

The role of B cells in cryptosporidiosis is controversial. Serum antibody responses may not always reflect properly the immune response at the level of the intestinal mucosa, and fecal antibody is subject to degradation. Early studies associated defects in humoral immunity with persistent or recurrent cryptosporidiosis, implying that B cells contribute to elimination of the parasite (41, 49, 92). However, in many cases, Ig deficiencies were coupled with either a functional complement defect (41) or immunosuppressive therapies (92), and hypogammaglobulinemia was accompanied by depressed serum levels of multiple Ig lines (49), suggesting that more than a single humoral immune defect is needed to increase susceptibility to chronic disease. Because many of the defects may reflect impaired T-cell function, it is not clear whether humoral defects are a major cause of increased susceptibility or rather a marker for other immune deficiencies which render individuals more susceptible to infection.

Evaluation of jejunal tissue taken from experimentally infected volunteers suggested that B cells are among the first lymphocytes to respond to *Cryptosporidium* infection. In the lamina propria, the number of B cells increases on day 3 postchallenge, peaks by day 9, and declines to baseline levels around day 14 (unpublished data). Antigen-specific B cells begin to appear in the circulation 5 days postchallenge, with a large proportion expressing the gut-homing integrin β7. They remain present for several weeks (S. M. Dann, unpublished data). Fecal IgA was detected in the stools of adult volunteers up to 6 weeks after infection (17). Serum IgG, IgA, and IgM antibody responses are usually directed against soluble or membrane-associated sporozoite proteins (65, 74); IgA reacts mostly to 17-kDa proteins (69, 76), IgM reacts mostly to 27-kDa proteins, and IgG reacts mostly to 17-, 27-, and 15-kDa proteins (69). Antibodies against 23-kDa proteins have also been recognized (76, 84). Antibodies against 27- and 17-kDa antigens were detected mainly in late serum samples during outbreaks (74). High levels of IgM to 27-kDa antigens and IgG to 17-kDa antigens prior to infection were associated with protection from illness but not infection, and the presence of IgG to 27-kDa antigens was associated with low levels of oocyst shedding (25, 69).

AIDS patients with cryptosporidiosis often have elevated levels of duodenal lamina propria IgA and IgM plasma cells (5). They also have higher total and specific fecal IgA levels than AIDS patients with other enteric infections or normal controls (5, 15). As the number of $CD4^+$ T cells decreases in HIV-infected individuals, mucosal antibody responses may become aberrant, and there may be increases in the levels of polyreactive T-cell-independent antibodies and serum-derived IgA and IgG (42, 75). Polyreactive antibodies may not be sufficient to clear infection. Although these findings suggest that antibodies have a minor role in elimination of the parasite, another interpretation is that T-cell-dependent antibodies are markers for a cellular immune response required for parasite control. Functional studies are needed to determine if antigen-specific B cells contribute to parasite control in humans.

T CELLS

Studies with humans, as well as studies with murine and other mammalian animal models, have suggested a crucial role for $CD4^+$ T cells in the immune response to *Cryptosporidium* infection. Cryptosporidiosis normally is self-limited in HIV-infected individuals with $CD4^+$ T-cell counts over 180 cells/μl and usually chronic in HIV-infected individuals with lower counts, and it may be fulminant in some patients with $CD4^+$ T-cell counts below 50 cells/μl (6, 24, 60). However, asymptomatic oocyst shedding has been noted in apparently healthy individuals and also in HIV-positive individuals (22, 39, 95). $CD4^+$ T cells are a major component of the human intestinal lamina propria (88) and are among the first T-cell populations to decrease after HIV infection (7, 55). Similarly, the recovery of an AIDS patient from cryptosporidiosis in response to highly active antiretroviral treatment was associated with increasing numbers of $CD4^+$ T cells in the intestinal mucosa (82).

The role, if any, of $CD8^+$ T cells in control of cryptosporidiosis is not clear. Cytotoxic $CD8^+$ T-cell responses are critical for clearance of most intracellular infections of cells other than professional antigen-presenting cells (34). However, murine studies suggested that $CD8^+$ T cells are not required for control of cryptosporidiosis (2, 89). In studies of the human immune response to recombinant *Cryptosporidium* antigens, we noted that IFN-γ was produced by both $CD4^+$ and $CD8^+$ T cells (73a). Similarly, we have noted cytotoxic T-cell responses eliminating *Cryptosporidium* from HLA-matched intestinal cell lines (B. Pantenburg, unpublished data). Further research investigating cytotoxic $CD8^+$ T cells is required.

IFN-γ-DEPENDENT IMMUNE RESPONSE AND CYTOKINES

In murine models, IFN-γ is a critical mediator of the innate and acquired immune responses controlling cryptosporidiosis (10, 52, 66, 87). Similarly, severe *Cryptosporidium*-associated diarrhea has been described for HIV-negative individuals with IFN-γ deficiency (28). After in vitro restimulation, lymphocytes from persons who had recovered from *Cryptosporidium* infection produced IFN-γ (28, 29), whereas lymphocytes from HIV-infected individuals with active cryptosporidiosis did not produce IFN-γ (29). Also, we noted expression of IFN-γ by lamina propria lymphocytes in the intestines of previously exposed (seropositive) individuals after oral rechallenge with oocysts (93). IFN-γ expression correlated with the lack of oocyst shedding (93). Thus, IFN-γ seems to be part of the human

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T-cell memory response to *Cryptosporidium*. However, we identified IFN-γ in the intestines of a minority of volunteers only after *Cryptosporidium* challenge, and IFN-γ expression was limited to the volunteers who appeared to be immune (that is, either seropositive or resistant to a challenge with a dose that was greater than the dose that would infect most volunteers) (93). Other groups failed to detect IFN-γ in stools or stimulated PBMC obtained at the time of acute infection (29, 44, 45). Thus, while IFN-γ seems to be critical for the memory response, other mechanisms may play a larger role in resolution of acute infection.

In murine models, IL-4 is involved in the immune response limiting *Cryptosporidium* infection (64). In vitro studies with human PBMC revealed expression of IL-4 and IFN-γ in a subset of T cells after stimulation with *Cryptosporidium* antigen (30). In human volunteers IL-4, like IFN-γ, was found to be expressed by lymphocytes in the lamina propria of infected individuals and was associated with memory immune responses; however, this expression did not correlate with oocyst shedding (79). IL-4 was expressed only in a subset of individuals who also produced IFN-γ, so its importance in humans remains unclear (79).

In studies to examine IFN-γ-independent pathways for clearance of *Cryptosporidium*, we noted increased expression of IL-15 in the jejunal mucosa of symptomatic individuals without prior sensitization to *Cryptosporidium* (79). IL-15 expression was inversely correlated with parasite burden. Thus, IL-15 seems to be part of the human innate immune response to *Cryptosporidium*, whereas IFN-γ appears to be associated with the T-cell memory immune response. In in vitro studies, we subsequently noted that IL-15 activates natural killer cells to eliminate intestinal *Cryptosporidium*-infected epithelial cells (18). Neither IFN-γ nor IL-15 was detected in the intestinal mucosa of AIDS patients with chronic uncontrolled cryptosporidiosis (71). Thus, there appear to be separate memory (associated with IFN-γ) and innate (associated with IL-15) immune responses involved in clearance of human cryptosporidiosis.

INFLAMMATORY MEDIATORS AND SUBSTANCE P

During *Cryptosporidium* infection the stools of Haitian and Brazilian children contained lactoferrin (3, 8, 44), a marker for fecal leukocytes. This finding suggests that *Cryptosporidium* induced an intestinal inflammatory response. The stools of infected Haitian and Brazilian children had markedly elevated levels of the receptor for the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) (3, 44, 45). TNF-α is believed to be involved in recruiting inflammatory cells to the intestinal mucosa (27, 50). PBMC of infected Haitian children expressed higher levels of TNF-α up to 6 months after infection when they were restimulated in vitro, suggesting that cryptosporidiosis triggers a systemic immune response which may lead to enhanced inflammation and possibly be responsible for worsening of malnutrition and stunting (45).

Both TNF-α and IL-1β are stimulators of prostaglandin production. *Cryptosporidium* infection of intestinal cell lines and human xenografts led to elevated levels of the prostaglandins E_2 and $F_{2\alpha}$ and their controlling protein, prostaglandin HS-2 (51). Although TNF-α and IL-1β themselves do not cause diarrhea, prostaglandins may contribute to diarrhea during infection by altering chloride secretion. However, they also have protective functions, including increasing intestinal mucin expression (63), which may interfere with sporozoite attachment (85). In experimentally infected adult volunteers, TNF-α and IL-1β mRNA have been found in the intestinal lamina propria (78), although TNF-α was not detected in the stools (3). This likely reflects the milder illness in volunteers than in AIDS patients or malnourished children. However, TNF-α was not associated with symptoms or oocyst shedding and thus did not seem to be an important mediator of diarrhea in human cryptosporidiosis (78).

The neuropeptide substance P is a member of the tachykinin family. It is made by nerves, endothelial cells, and cells of the immune system (14, 31, 38, 58, 91). Substance P plays an important role in stimulating the production of proinflammatory cytokines like IFN-γ, IL-1β, IL-6, and TNF-α and immune-mediated inflammatory processes (4, 16, 23, 54, 56, 61). It also induces Cl^- ion secretion in human gastrointestinal explants (77). Elevated substance P expression has been reported in the intestinal tissues from patients with inflammatory bowel disease and correlates with disease activity (46).

We noted increased expression of substance P in intestinal tissues from patients with symptomatic cases of cryptosporidiosis but not in intestinal tissues from controls (81). AIDS patients with severe diarrhea expressed more substance P mRNA and protein than patients with mild illness. Substance P was produced by intraepithelial lymphocytes and lymphocytes or monocytes in the intestinal lamina propria (81). Similarly, substance P was found in the intestines of symptomatic *Cryptosporidium*-infected macaques (37). In these studies, increased expression of substance P and its receptor, NK1, was associated with elevated basal intestinal chloride secretion and glucose malabsorption, further supporting the hypothesis that substance P is responsible for the symptoms accompanying cryptosporidiosis (37).

ANTI-INFLAMMATORY CYTOKINES

Interestingly, *Cryptosporidium* infection also triggers expression of anti-inflammatory cytokines. IL-10 was found in the stools of infected Haitian children (44). IL-10 is secreted by a variety of cells in the intestinal mucosa and antagonizes mucosal inflammatory and immune responses (68). Thus, it may prevent excessive, potentially host-threatening immune responses during the course of infection.

Transforming growth factor β (TGF-β) mRNA was detected in the intestinal epithelium of some patients with symptoms and oocyst shedding (80), but in most cases it was detected only after resolution of symptoms and oocyst shedding. TGF-β has previously been found to reduce intestinal inflammation (73) and to mediate repair of epithelial monolayers damaged by *Cryptosporidium* infection (72). Interestingly, both IL-10 and TGF-β promote Ig class switching of human B cells towards production of IgA (19). Thus, IL-10 and TGF-β may be key factors for repairing the intestinal epithelium after cryptosporidiosis.

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SUMMARY

Immunity to *Cryptosporidium* involves both innate and adaptive immune responses. Initially, chemokines such as CXCL-10 and perhaps CXCL-8 attract effector cells to the site of infection. Activation of an early immune response by IL-15 is critical for initial clearance of the parasite. $CD4^+$ T cells and IFN-γ play key roles in the human memory response. The function of B cells and $CD8^+$ T cells requires further research.

The intestinal inflammatory response seems to mediate diarrhea. Substance P is likely a key mediator of gastrointestinal symptoms in human infection; prostaglandins have been implicated in animal models, but their role in human infection is unclear. TGF-β and IL-10 are likely involved in anti-inflammatory and healing processes. They may also lead to generation of secretory IgA, which may prevent reinfection.

Despite the difficulties of investigating human intestinal immune responses, such studies provide important insights into the human mucosal immune response. Since cryptosporidiosis has a significant impact on the health of immunocompromised patients and children in developing countries, further study of the pathogenesis and host immune response in patients with cryptosporidiosis is warranted. *Cryptosporidium* infection may also provide an important model for dissecting the human intestinal mucosal immune response towards other pathogens and for studying aberrant responses in inflammatory bowel disease.

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