Cryptosporidium Parvum-Induced Inflammatory Bowel Disease of TCR-β- x TCR-δ-Deficient Mice

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Cryptosporidium Parvum-Induced Inflammatory Bowel Disease of TCR-β- x TCR-δ-Deficient Mice

Abstract
Experimental inoculation of neonatal immunocompetent strains of mice with Cryptosporidium parvum results in a transient, noninflammatory enteric infection. In the present study, we show that inoculation of mice deficient in a 3 and γ8 T cells (TCR-3- X TCR-8-deficient mice) with C. parvum results in persistent infection and severe inflammatory bowel disease-like lesions. The most severe lesions in these mice were in the cecum with similar yet less severe lesions in the ileum and proximal colon. The most notable aspect of the histopathology was glandular hyperplasia with abscess formation, extensive fibrosis of the lamina propria with infiltrates of predominately polymorphonuclear cells and macrophages, and a few small aggregates of B cells. Persistently infected mice also developed extensive hepatic periportal fibrosis in association with C. parvum colonization of bile ducts. Lesions observed in TCR- 3- X TCR-8-deficient mice were markedly different than previously described lesions detected in C. parvum-infected TCR-o-deficient mice. Cryptosporidium parvum-infected TCR-o-deficient mice have extensive infiltrations of B cells, whereas TCR-P3- X TCR-8-deficient mice had only a few small aggregates of B cells. These findings indicate that although γ8 T cells are not necessary for induction of intestinal inflammation in C. parvum-infected o(4 T- cell-deficient mice, their presence does alter the morphology of the ensuing lesion.

Disciplines
Veterinary Microbiology and Immunobiology | Veterinary Pathology and Pathobiology | Veterinary Preventive Medicine, Epidemiology, and Public Health

Comments

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CRYPTOSPORIDIUM PARVUM-INDUCED INFLAMMATORY BOWEL DISEASE OF TCR-β- X TCR-δ-DEFICIENT MICE

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ABSTRACT: Experimental inoculation of neonatal immunocompetent strains of mice with Cryptosporidium parvum results in a transient, noninflammatory enteric infection. In the present study, we show that inoculation of mice deficient in αβ and γδ T cells (TCR-β- X TCR-δ-deficient mice) with C. parvum results in persistent infection and severe inflammatory bowel disease-like lesions. The most severe lesions in these mice were in the cecum with similar yet less severe lesions in the ileum and proximal colon. The most notable aspect of the histopathology was glandular hyperplasia with abscess formation, extensive fibrosis of the lamina propria with infiltrates of predominately polymorphonuclear cells and macrophages, and a few small aggregates of B cells. Persistently infected mice also developed extensive hepatic periportal fibrosis in association with C. parvum colonization of bile ducts. Lesions observed in TCR-β- X TCR-δ-deficient mice were markedly different than previously described lesions detected in C. parvum-infected TCR-α-deficient mice. Cryptosporidium parvum-infected TCR-α-deficient mice have extensive infiltrations of B cells, whereas TCR-β- X TCR-δ-deficient mice had only a few small aggregates of B cells. These findings indicate that although γδ T cells are not necessary for induction of intestinal inflammation in C. parvum-infected αβ T-cell-deficient mice, their presence does alter the morphology of the ensuing lesion.

Cryptosporidium parvum is an intracellular protozoan parasite that infects various mammals, including humans and mice (Fayer et al., 1997). T-cell-mediated immune responses are essential for clearance of C. parvum infection (Heine et al., 1984; Ungar et al., 1990; Mead et al., 1991; Kuhls et al., 1992). More specifically, T-helper cells (CD4+) and interferon-γ limit the duration and severity of infection, respectively (Ungar et al., 1991; Chen et al., 1993; Aguirre et al., 1994; Theodos et al., 1997). In addition, αβ T cells are required for the clearance of C. parvum; experimental inoculation of TCR-α-deficient mice with C. parvum results in persistent infection and an accelerated onset of an inflammatory bowel disease (IBD)-like syndrome that occurs naturally in this strain of mice (Waters and Harp, 1996; Waters et al., 1997). Flora-bearing TCR-α-deficient mice spontaneously develop IBD at 4–5 mo of age, whereas C. parvum infection induces IBD as early as 4 wk of age (Mombaerts et al., 1993; Waters et al., 1997). Germ-free TCR-α-deficient mice do not develop the spontaneous form of IBD (Dianda et al., 1997). However, experimental inoculation of germ-free TCR-α-deficient mice with C. parvum results in persistent infection and IBD (Sacco et al., 1998). In contrast to αβ T cells, γδ T cells are not required for clearance of C. parvum infection (Waters and Harp, 1996). Infection of neonatal immunocompetent strains of mice results in a transient infection without detectable intestinal lesions (Sherwood et al., 1982; Fayer et al., 1997). Adult immunocompetent strains of mice are generally not susceptible to infection with C. parvum (Fayer et al., 1997).

A remarkable component of the intestinal IBD lesions of TCR-α-deficient mice is mononuclear cell infiltration within the cecal lamina propria. In flora-bearing TCR-α-deficient mice, these infiltrates are predominately B cells and γδ T cells, with a small population of TCR αβ- cells and natural killer (NK) cells (Mombaerts et al., 1993; Takahashi et al., 1997; Waters et al., 1997). However, in germ-free TCR-α-deficient mice with C. parvum-induced IBD, only B220+ IgD+ B cell infiltrates have been detected (Sacco et al., 1998). These infiltrates of B cells are present in distinct foci (reminiscent of germinal centers), whereas infiltrates of lymphocytes in flora-bearing mice are more diffusely distributed. The accumulation of B cells within these lesions during persistent infection provides further evidence supporting the hypothesis that B cells have a minimal role in the resolution of C. parvum infection (Taghi-Kilani et al., 1990).

Extraintestinal sites of C. parvum colonization occur in several immunodeficient mouse strains (Mead et al., 1991; Cosyns et al., 1998). Hepatic involvement in these strains of mice is of particular interest because C. parvum infection of acquired immune deficiency syndrome patients often results in biliary tract colonization and associated hepatic disease (Casemore et al., 1998). In addition, extraintestinal cryptosporidiosis often contributes to the mortality of infected individuals and may be a source for recurrent infections.

In the present study, we show that TCR-β- X TCR-δ-deficient mice inoculated with C. parvum become persistently infected with the parasite and subsequently develop inflammatory intestinal lesions. Lesions in C. parvum-infected TCR-β- X TCR-δ-deficient mice are similar to those described in C. parvum-infected congenitally athymic mice that also lack αβ and thymically derived γδ T cells (Heine et al., 1984). However, athymic mice have a large population of extrathymically derived intestinal γδ T cells (Allison, 1993). Thus, the present study definitively shows that γδ T cells within the intestine are not necessary for development of IBD-like lesions in C. parvum-infected TCR-α-deficient mice.
MATERIALS AND METHODS

Animals

Breeding pairs of TCR-β- × TCR-δ-deficient and C57BL/6J control mice were purchased from Jackson Laboratories (Bar Harbor, Maine). A breeding colony was established and maintained at the National Animal Disease Center (Ames, Iowa) for the generation of mice for experiments. Mice received tap water and rodent chow ad libitum (Harlan Teklad, Madison, Wisconsin). Flow cytometric analyses of spleen cells confirmed deficiency of αβ and γδ T cells in TCR-β- × TCR-δ-deficient mice and normal numbers of αβ and γδ T cells in C57BL/6J control mice (data not shown).

Parasites and oral inoculation

Purified oocysts were isolated from feces collected from calves experimentally inoculated with C. parvum oocysts by a method described previously (Harp et al., 1992). Oral inoculation of mice consisted of 10⁶ oocysts in 100 μl of 0.15 M phosphate-buffered saline solution. Mice were inoculated with C. parvum oocysts at 1 wk of age by gavage using a 26-gauge needle with tygon tubing fitted over the end of the needle. Experimental groups included: TCR-β- × TCR-δ-deficient mice inoculated with C. parvum (experimental), C57BL/6J mice inoculated with C. parvum (strain-matched controls), and noninfected TCR-β- × TCR-δ-deficient mice (noninfected controls). For assessment of C. parvum colonization, fecal pellets were collected by placing individual mice into beakers until they defecated. Fresh fecal pellets were then smeared onto glass slides, stained with carbol fuchsin, and examined for the presence of C. parvum oocysts.

Histology

At the end of the experiment, mice were killed and intestinal sections from the liver, distal ileum, cecum, and proximal colon were fixed in formalin and embedded in paraffin. Sections were cut at a thickness of 4 μm, stained with hematoxylin and eosin (H&E), and examined microscopically for C. parvum and any histopathology.

Immunohistochemistry

Cecal sections were snap frozen in O.C.T. compound (Miles, Elkhart, Indiana) and stored at −70 C for immunohistochemistry. Frozen sections were equilibrated to −20 C and cut using a microtome (Reichert, Buffalo, New York) at a thickness of 8 μm. Slides were placed on poly-l-lysine-coated slides, fixed with 95% ethanol, and frozen to −70 C for later use. Frozen sections on slides were allowed to warm up to room temperature (RT) for 30 min, rehydrated in Tris buffer for 15 min, and blocked with 5% normal serum for 20 min at RT. Biotinylated anti-mouse primary antibodies diluted 1:100 in Tris buffer plus 3% bovine serum albumin were added to the slides and incubated overnight at 4 C. Primary antibodies were hamster anti-mouse TCR-β chain (clone H57-597), hamster anti-mouse γδ TCR (clone GL-3), mouse anti-mouse CD161 (NK cells, clone PK 136), mouse anti-mouse IgD (clone 217-170), rat anti-mouse CD5 (Ly-1, clone 53-7.3), rat anti-mouse CD11b (Mac-1 α chain, clone M1/70), and rat anti-mouse B220 (B cells, clone RA3-6B2). All primary antibodies were obtained from PharMingen, San Diego, California, except RA3-6B2 that was purified from supernatants of hybridoma cultures and biotinylated using standard procedures. Slides were then washed with Tris buffer and flooded with streptavidin–peroxidase (Kirkegaard and Perry Laboratories, Inc., Gaithersburg, Maryland), incubated 2 h at RT, washed with Tris buffer, flooded with diaminobenzidine substrate/chromagen (Biomeda, Foster City, California) for 10 min at RT, washed, and counterstained with light green (Biomeda) for 2 min. Slides were then washed with tap water, washed with distilled water, and mounted with Immuno-Mount preparation (Shandon, Pittsburgh, Pennsylvania).

RESULTS

Infection dynamics, clinical signs, and gross pathology

TCR-β- × TCR-δ-deficient mice inoculated with C. parvum at 1 wk of age developed a persistent infection, whereas C57BL/6J mice inoculated with C. parvum at 1 wk of age were only transiently infected. Persistently infected TCR-β- × TCR-δ-deficient mice exhibited varying degrees of severity of clinical signs of IBD ranging from a progressive wasting syndrome with a hunched over posture to no clinical signs. Clinical signs of IBD were observed as early as 2 wk postinfection. Regardless of the clinical expression of disease, all TCR-β- × TCR-δ-deficient mice inoculated with C. parvum had persistent C. parvum infection and histologic evidence of intestinal inflammation. Gross lesions included severe edema of the distal small intestine and entire large intestine with particularly severe edema of the cecum. Clinical signs and gross pathology increased in severity with duration of infection. Two TCR-β- × TCR-δ-deficient mice died 21–28 days postinoculation. In contrast, C57BL/6J control mice (infected) and age-matched noninfected TCR-β- × TCR-δ-deficient mice had no clinical signs of infection and no gross pathology of the intestinal tract. Clinical signs and gross lesions detected in C. parvum-infected TCR-β- × TCR-δ-deficient mice were similar to those detected in a prior study of C. parvum-infected TCR-α-deficient mice (Waters et al., 1997).

Histopathology

Ceca from 9-wk-old TCR-β- × TCR-δ-deficient mice infected with C. parvum at 1 wk of age were diffusely thickened and contained numerous dilated, often cystic glands, variably filled with necrotic cell debris and cryptosporidia, and lined by flattened enterocytes (Fig. 1A). The surface epithelium at the extrusion zone was distorted and protruded into the lumen excessively. The lamina propria was expanded due to infiltrates of numerous macrophages, fibroblasts, and nodular aggregates of lymphocytes. Numerous gland abscesses were seen containing necrotic cell debris, neutrophils, and cryptosporidia. The submucosa was multifocally expanded due to edema. Similar lesions, but less severe, were noted in the proximal colon. Distal ileum also contained lesions of mild diffuse crypt hyperplasia and infiltrates of low numbers of neutrophils, macrophages, and lymphocytes within the lamina propria. The surface epithelium of the ileum was distorted at the extrusion zone and protruded into the lumen. Numerous cryptosporidia were seen associated with villous enterocytes.

Liver sections from 9-wk-old TCR-β- × TCR-δ-deficient mice infected with C. parvum at 1-wk age contained periportal infiltrates of macrophages and lymphocytes, with moderate fibrosis (Fig. 1B). Infiltrates surrounded irregularly dilated bile ductules. Bile ductules were filled with intraluminal neutrophils and cryptosporidia and were lined by hyperplastic epithelium. The wall of the gallbladder was diffusely thickened due to deposition of large amounts of collagen and infiltrates of moderate numbers of lymphocytes and macrophages. The gallbladder lumen contained cryptosporidia and low numbers of neutrophils, macrophages, and lymphocytes.

Lesions in 3- and 5-wk-old (Fig. 1C) mice were similar to those seen in older mice but less severe. Intestinal sections from noninfected, age-matched TCR-β- × TCR-δ-deficient mice (Fig. 1D) and C57BL/6J control mice were normal and no cryptosporidia were detected. Cryptosporidium parvum-infected C57BL/6J mice had no detectable lesions (light microscopic) at any time point postinfection. Intestinal sections were also obtained from a TCR-β- × TCR-δ-deficient dam of an infected
Figure 1. Histopathological features of intestinal inflammation in ceca and liver from TCR-β- × TCR-δ-deficient mice. Photomicrographs of sections of cecum from 9-wk-old TCR-β- × TCR-δ-deficient mouse infected with Cryptosporidium parvum at 1 wk of age (A), liver from a 9-wk-old TCR-β- × TCR-δ-deficient mouse infected with C. parvum at 1 wk of age (B), cecum from 5-wk-old TCR-β- × TCR-δ-deficient mouse infected with C. parvum at 1 wk of age (C), and cecum from noninfected 9-wk-old TCR-β- × TCR-δ-deficient mouse (D). Note increased thickness of mucosa of A and C as compared to D. Note hyperplastic and dilated glands in 1a (short arrows) and gland abscess in A (long arrow) and C (arrow). Note presence of C. parvum (arrows) in bile ductules of liver in B. Lesions were not seen in infected C57BL/6J mice (not shown). H&E staining with bar on A = 100 μm, bar on B = 35 μm, and bar on C and D = 55 μm.

Numerous C. parvum were detected in intestinal sections; indicating vertical transmission from pups to dam and adult susceptibility to infection. Hyperplastic and inflammatory intestinal lesions were also present in the infected dam.

Immunohistochemistry

Staining of serial sections of ceca for lymphocyte surface antigens revealed occasional small aggregates of B220+, IgD+ infiltrates (Fig. 2A) and extensive infiltration of Mac-1+ cells (Fig. 2B, C) within the lamina propria of C. parvum-infected TCR-β- × TCR-δ-deficient mice. αβ T cells, γδ T cells, Ly-1+ cells, and NK cells were not detected in cecal sections from infected TCR-β- × TCR-δ-deficient mice. Fewer numbers of B cells (B220+, IgD+) were detected in ceca lamina propria from infected TCR-β- × TCR-δ-deficient mice as compared to numbers of B cells detected in cecal lamina propria from C. parvum-infected TCR-α-deficient mice (W. Waters, unpubl. obs.). Occasional submucosal lymphoid aggregates were detected in ceca from both infected and noninfected TCR-β- × TCR-δ-deficient mice. These aggregates consisted of B220+, IgD+ cells.
DISCUSSION

IBD of humans is characterized by 2 diseases of unknown etiology, Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD in humans has not been determined. However, it has been postulated that immunologic dysfunction, or infectious etiologies, or both, contribute to the induction of disease (Soppi et al., 1988; De Vos et al., 1997; Fiocchi, 1997). For instance, colonic tissue collected from individuals suffering from IBD often has increased numbers of lamina propria lymphocytes and increased mucosal expression of tumor-associated antigens, decreased T-cell suppressor activity, macrophage dysfunction, and mucin alterations (Fiocchi et al., 1979; Goodacre and Bienenstock, 1982; Haviland et al., 1988; Okabe et al., 1988; Soppi et al., 1988). These changes differ among patients depending upon the chronicity of the disease and distribution of lesions, i.e., CD versus UC. Likewise, the premise that immunologic dysfunction contributes to the onset of IBD is supported by several experimental mouse models of this disease (Kuhn et al., 1993; Mombaerts et al., 1993; Sadlack et al., 1993; Powrie et al., 1994; Elson et al., 1995). With these models, distinctly differing immunologic defects result in similar sequelae.

Spontaneous IBD has been demonstrated in TCR-α-deficient, TCR-β-deficient, TCR-β-×TCR-δ-deficient, and major histocompatibility complex (MHC) class II-deficient mice but not in recombination-activating gene 1-deficient, TCR-δ-deficient, or severe combined immunodeficient (SCID) mice (Mombaerts et al., 1993). With regard to IBD, a common feature of the susceptible immunocompromised strains of mice studied to date is an intact B-cell population and deficient CD4+ αβ T-cell population. Likewise, C. parvum-induced IBD occurs in TCR-α-deficient, TCR-β-×TCR-δ-deficient (findings from the present study), MHC class II-deficient, and nude mice but not in TCR-δ-deficient mice (Heine et al., 1984; Aguirre et al., 1994; Waters et al., 1997). Cryptosporidium parvum infection of SCID mice also induces intestinal lesions; however, lesions are less severe as compared to lesions in TCR-α-deficient, TCR-β-×TCR-δ-deficient, MHC class II-deficient, and nude mice. In addition, C. parvum infection of SCID mice requires 3–4 mo for lesion formation as compared to 3–4 wk for lesion formation in these other strains (Mead et al., 1991, 1994; Harp et al., 1992; Kuhl, et al., 1992). Thus, like the spontaneous form of IBD, it appears that mice deficient in CD4+ αβ T cells yet with an intact B-cell population are susceptible to C. parvum-induced IBD.

Cryptosporidium parvum infection of immunocompetent strains of mice does not result in intestinal lesions. Strains of mice lacking CD4+ αβ T cells are unable to control C. parvum infection, resulting in chronic inflammation and IBD. B cells may be involved in lesion development in these strains of mice because B cells are detected within affected tissues. Others have shown that the number of B cells producing IgG1, IgG2a, and IgA are increased in intestinal tissues of TCR-α-deficient mice.

**FIGURE 2.** Immunohistochemical staining of leukocytes in the cecal lamina propria of TCR-β × TCR-δ-deficient mice infected with Cryptosporidium parvum. Photomicrographs of sections of cecum from 9-wk-old TCR-β × TCR-δ-deficient mouse infected with C. parvum at 1 wk of age stained with RA3-6B2 (B220) (A) or M1/70 (Mac-1 chain) (B, C). Note B220+ cells in A are present in distinct aggregates (arrow). Similar staining patterns as depicted in A were detected when serial sections were stained with 217–170 (IgD+) (not shown). Note extensive infiltration of lamina propria by Mac-1+ cells (arrows) in B and C. Area depicted in B with an arrow is shown at a higher magnification in C and g denotes gland lumina. Immunoperoxidase staining with bar on A = 55 μm, bar on B = 80 μm, and bar on C = 35 μm.
with IBD (Mizoguchi, Mizoguchi, Chiba, and Bhan, 1996). It has been postulated that the observed IBD could result from mucosal insult by autoantibodies (Mombaerts et al., 1993). Indeed, increased numbers of mesenteric lymph node B cells secreting autoantibodies (IgG2a) to tropomyosin were detected in TCR-α-deficient mice with IBD (Mizoguchi, Mizoguchi, Chiba, Spiekermann et al., 1996). Thus, loss of oral tolerance to dietary or microbial antigens as a result of a lack of αβ T-cell regulation of B cells could lead to an autoimmune attack against the intestinal epithelium, possibly due to cross-reactive antibodies.

Interestingly, TCR-β- × TCR-δ-deficient mice do not develop prominent foci of B cells within their cecal lamina propria as are detected in C. parvum-infected, germ-free TCR-α-deficient mice or the more randomly distributed yet prominent infiltrates of B cells as are detected in C. parvum-infected, flora-bearing TCR-α-deficient mice. This finding implies that the presence of γδ T cells may influence the nature of the lesion by regulating B-cell trafficking or proliferation. γδ T cells can sustain the production of germinal centers and lymphoid follicles and provide help for immunoglobulin isotype switching, ordinarily considered signatures of αβ T-cell–B-cell collaboration (Dianda et al., 1996; Wen et al., 1996). However, γδ T-cell help has been associated with an increased production of generalized antibodies that are not specific for the relevant pathogen (Pao et al., 1996). These generalized antibodies may be involved in the development of autoimmunity and IBD. Alternatively, γδ T cells may proliferate in response to host-derived antigens as a result of inflammation due to persistent C. parvum infection (Mukasa et al., 1997). Thus, even though γδ T cells are not required for lesion development in C. parvum-infected TCR-α-deficient mice, they may influence the type and severity of lesion that develops.

Recently, it has been proposed that CD4+, TCR αβ+ T cells mediate development of the spontaneous form of IBD in TCR-α-deficient mice (Takahasi et al., 1997). Increased numbers of these cells were detected in TCR-α-deficient mice with IBD and this increase accompanied an elevated secretion of anti-self antibody (Takahasi et al., 1997). In that study, it was speculated that TCR αβ+ T cells may help B cells produce autoantibodies, thus initiating IBD. Furthermore, these cells (CD4+, TCR αβ+ T cells) have been shown to be the primary cell necessary for germinal center formation in TCR-α-deficient mice (Wen et al., 1996). TCR-β- × TCR-δ-deficient mice do not have TCR αβ+ T cells (Mombaerts et al., 1992). Thus, in this model, C. parvum induction of IBD-like lesions is not dependent upon TCR αβ+ T cells.

With persistent C. parvum infection, TCR-β- × TCR-δ-deficient mice developed severe hepatic periportal fibrosis due to C. parvum colonization of bile ducts. Other immune-deficient strains of mice also have biliary tract colonization upon chronic infection with C. parvum (Mead et al., 1991; Cosyns et al., 1998). However, persistently infected TCR-α-deficient mice do not develop hepatic C. parvum infection (Waters et al., 1997). Thus, γδ and/or TCR αβ+ T cells may be involved in limiting biliary tract colonization by C. parvum.

In conclusion, we have shown that experimental inoculation of TCR-β- × TCR-δ-deficient mice with C. parvum results in persistent infection and induction of IBD. These results indicate that neither γδ T cells nor TCR αβ+ T cells are necessary for C. parvum-induced IBD. Furthermore, if C. parvum-induced IBD is immune mediated, these findings suggest that B cells are involved in lesion formation.

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LITERATURE CITED


