Fulminant Amoebic Colitis: Role of the Innate and Adaptive Immune Responses

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1. Introduction

About 10% of the world population is affected by an invasion of the colon by Entamoeba histolytica (E. histolytica) that results in intestinal amebiasis. This pathogenesis is an important cause of death worldwide, ranking fourth among parasite related fatalities, behind malaria, Chagas disease and Leshmaniasis. Clinically speaking, E. histolytica causes amoebic dysentery, ameboma, amoebic appendicitis and fulminant amoebic colitis (FAC) (Espinosa-Cantellano & Martínez-Palomino, 2000; Pérez-Tamayo, 1986; Prathap & Gilman, 1970).

Amoebic dysentery, or ulcerative colitis, affects 90% of the population that is invaded by E. histolytica. By means of adhesins, ameboholes and proteases, amebas induce the formation of two kinds of ulcers: nodular and irregular. Nodular ulcers are round, measuring 0.1 to 0.5 cm in diameter, and are slightly elevated compared to surrounding tissue. The necrotic center can appear sunken and hemorrhagic, but more frequently is covered with yellowish mucous material (Fig. 1, arrows) the ulcer is surrounded by edematous mucosa. Chronic and abundant nodular ulcers become irregular ulcers (Fig. 1, asterisk) that affect a greater area of the colon and can reach up to 5 cm in diameter. Irregular ulcers, surrounded by edematous mucosa, acellular proteinaceous material, erythrocytes and strand of fibrins, can even invade the submucosa cap, causing abundant infiltrate of neutrophils and macrophages, and a scarce quantity of eosinophils (Fig. 1, asterisk) (Espinosa-Cantellano & Martínez-Palomino, 2000). An appropriate treatment of metronidazole or its derivatives normally cures this type of amebiasis satisfactorily.

During intestinal amebiasis, it is unusual to find colonic ameboma, which is characterized by a great mass of well-defined tissue on the wall of the intestinal lumen. The ulcerated mucosa is a thin layer and the other layers of the colon are thicker than normal, edematous and hemorrhagic. The peritoneum is affected and there are adherences between one or more loops of the small intestine.
Another clinical manifestation of intestinal amebiasis is amebic appendicitis, in which there are nodular ulcers in the mucosa of the organ accompanied by acute inflammation. However, the histopathology is similar to other appendicitis and the parasite can only be detected through microscopic intestinal cuts (Pérez-Tamayo, 1986).

Fig. 1. Amebic nodular necrotic ulcers (arrows) and amebic irregular ulcers (asterisk) in human colon (Espinosa-Cantellano & Martínez Palomo, 2000).

FAC is the rarest intestinal amebiasis, with a morbidity rate of 0.01% and a mortality rate of 40 to 100%. It is characterized by the following clinical manifestations: stomach pain, diarrhea, rectal bleeding, peritonitis, fever and abdominal pain (Chun et al., 1994; Takahashi et al., 1997). In the colon of patients, FAC is characterized by inflammation and ulcerous necrotic lesions that extend to great areas, on occasions covering the entire organ (Chun et al., 1994; Natarajan et al., 2000). Various researchers have queried about the role played by the immune response in this pathology (Ventura-Juárez et al., 2002, 2007). For instance, perhaps the inflammatory response has the objective of eliminating the amebas, only to end up participating in the pathogenesis (Kammanadiminti et al., 2007; Seydel et al., 1998).

Different hypothesis have been proposed regarding the role of the immune response during the FAC:

a. The immune response of the host is inappropriate (Seydel et al., 1997, 1998, 2000).

b. The trophozoites of *E. histolytica* are capable of inhibiting the action of complement proteins (Petri et al., 2002; Que et al., 2003; Que & Reed, 2000).

c. Inflammation is induced by cytokines of colonic epithelial cells (Eckmann et al., 1995; Kammanadiminti et al., 2007; Seydel et al., 1997; Yu & Chadee, 1997).

d. A type 2 (Th2) immune response predominates during amebic colitis.
It is important to note that there are scant reports on the interaction between *E. histolytica* and elements of the immune response during FAC. Consequently, the physiopathology of this disorder deserves to be deeply analyzed. Like intestinal or hepatic amebiasis, a hallmark of FAC is that trophozoites of *E. histolytica* are capable of migrating through the intestine and of provoking perforations in intestinal tissue that cannot be repaired. An important question is why these lesions can be formed and later cannot be repaired, in spite of or perhaps to some extent because of the immune response.

On the other hand, there are other ways in which the immune response during the pathogenesis of FAC differs from that which occurs as a result of other types of amebiasis. With FAC there is never any contact between neutrophils and *E. histolytica* trophozoites, decreased levels exist of macrophages, eosinophils, mast cell, CD8 cells and IgM producing plasma cells, and INFγ is apparently not produced. Several researchers have suggested that it is precisely these special conditions of the immune response to FAC that are responsible for ability of *E. histolytica* trophozoites to induce mortal damage to the patient (Prathap & Gilman, 1970; Shetty et al., 1990; Ximénez et al., 1990; Haque et al., 2001; Valenzuela et al., 2001; Sánchez-Guillén et al., 2002; Ventura-Juárez et al., 2003). However, there are other elements of the immune response to FAC, as well as to other forms of amebiasis, that have yet to be studied, among which are IL-8, IL-4, IL-10, TGFβ and NK cells, nevertheless, the cellular immunological factors that underlie the pathogenesis of FAC, especially in the context of host-parasite interactions, are currently unknown. Therefore, the aim of this chapter is to approach the study of FAC firstly from a morphological point of view and secondly by considering the implications of the inflammatory and immune response in the host-parasite relation.

2. Materials and methods

2.1 Immunohistochemical techniques

Specimens were placed in 10% formaldehyde and processed by conventional histological technic for paraffin sectioning. Six-micron thick slices of healthy or FAC intestine specimens were deparaffinized and rehydrated with phosphate-buffered saline (PBS). The activity of endogenous peroxidase was inhibited for 30 min with a 1% H2O2 solution in 100% methanol. The specimens were then rehydrated in a graded alcohol series and placed in PBS for 5 min. An antigen-unmasking solution (Vector Laboratories, Inc., Burlingame, CA, USA) was applied at vapor pressure for 1 min. Next, the samples were washed in PBS for 5 min, incubated in 20% fetal bovine serum (Hyclone Laboratories, Logan, UT, USA) in PBS for 30 min and washed three times PBS-0.25% Tween for 10 min. The slides of infected and uninfected tissue were then incubated with the primary antibody for 12 h using the primary antibodies described in table 1.

After incubation all slides were washed with PBS-0.25% Tween for 10 min, then incubated for 1 h at 37 °C, at room temperature using the secondary antibodies: Anti-Polyvalent HRP Ultra Vision Plus Large Volume Detection System (Thermo Scientific TP-060-HLX). Once this incubation was finished, the slides were washed with PBS-0.25%-Tween for 10 min, and peroxidase activity was developed with diaminobenzidine for 5 min. Finally, the slides were counterstained for 7 min with 1:10 Harris’ haematoxylin diluted in distilled water, washed with water, dehydrated in a graded alcohol series, passed twice through xylene and covered.
with synthetic resin. Control slides were prepared following the same protocol for each antibody, with the exception that the primary antibody was substituted with a nonspecific IgG antibody. Finally, immune-stained cells were counted from five slides for each sample. Five 40x fields were analyzed for each slide (viewing each corner and the center) with the aid of Image Pro-Plus imaging software (Image Pro Plus, Media Cybernetics, Silver Spring, MD, USA).

<table>
<thead>
<tr>
<th>Primary antibody</th>
<th>Host</th>
<th>Antigen recognized</th>
<th>dilution</th>
<th>Trademark</th>
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<tr>
<td>Human CD15 (Neutrophils)</td>
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<td>Lacto-N-fucose pentaosyl</td>
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<td>Human CD68 (Macrophages)</td>
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<td>E. histolytica</td>
<td>Rb</td>
<td></td>
<td>1:500</td>
<td>Obtained in our laboratory</td>
</tr>
<tr>
<td>Human IgG</td>
<td>Gt</td>
<td>Heavy chains of human</td>
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<td>Gt</td>
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<td>Human IgM</td>
<td>Gt</td>
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<td>Human CD59</td>
<td>Ms</td>
<td>Glycoprotein 17a 25kDa</td>
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Table 1. Antibodies used for the localization of antigens. Mouse (Ms), rabbit (Rb), rat (Rt) and goat (Gt).

2.2 Histochemical technique

2.2.1 Eosinophil staining

In order to detect eosinophils in colonic tissue sections, paraffin embedded specimens were used. They were deparaffinized and rehydrated in a graded alcohol series to distilled water,
then stained with Harris’ haematoxylin for 1 min and washed in distilled water. Afterward, the slides were stained with 1.5% erythrosin B in 0.1% of glycine buffer, pH 10, for 30 min, and, to remove the excess stain in the specimen, they were placed in a quick bath of 70% ethanol in Coplin jars. Finally, the specimens were dehydrated and covered with synthetic resin.

### 2.2.2 Mast cell staining

Six-micron-thick slices of specimens of normal or infected large intestine were deparaffinized and rehydrated with PBS. They were stained with Harris’ haematoxylin for 5 min, washed in distilled water, and incubated for 1 hour with 0.7% toluidine blue in 0.2% acetic acid/sodium acetate. The slides were quickly dehydrated in 70% alcohol, passed to 100% alcohol for 5 min, passed twice through xylene and covered with synthetic resin.

### 3. Background of fulminant amoebic colitis

Although the histopathological characteristics of FAC are currently very well defined, the role played by inflammatory cells and other cells of the immune response during this usually mortal pathological process is unknown. Masliah & Perez-Tamayo (1984) made an analysis based on 10 patients with FAC characterized by an acute and fatal course of illness. They did staining with Haematoxilin and Eosin (H & E), and reaction with periodic acid Schiff (PAS), finding extensive necrosis with scarce inflammation on the colon walls, in the midst of abundant amebas in process of disintegration. The amoebic ulcers healed without scar tissue. The authors described the histopathological damage in four forms: a) ulcers with *E. histolytica* in the mucosa-submucosa showing inflammation and/or necrosis, but without *E. histolytica* in the external muscular layer; b) *E. histolytica* in mucosa-submucosa and in the *muscularis mucosae*, without alterations in the external muscular layer; c) *E. histolytica* in the mucosa-submucosa and the external muscular layer; d) necrosis in the mucosa-submucosa and external muscular layer, but without *E. histolytica*. In each case the *E. histolytica* trophozoites were found to be more abundant in the mucosa-submucosa than the external muscular layer.

A decade later, Chun et al. (1994) analyzed four patients who underwent surgery for acute abdominal pain, practicing a surgical resection of colon. Immediately after surgery there was 50% mortality. Macroscopically they discovered a pseudomembranous colitis characterized by an extremely friable intestinal wall, and the mucosa with innumerable ulcers covered by yellowish-green pseudomembranes. Although intact, the mucosa among the ulcers was hyperemic and the serous membrane presented fibrinopurulent exudate and discoloration of the tissue. By using H & E and immunohistochemical techniques, the lesion was described as acute transmural necrotizing colitis, where alterations were not found in the Lieberkhün crypts, but were indeed found in the lamina propria adjacent to the edges of the ulcers, with abundant lymphocytes and plasma cells. The pseudomembranes that covered the ulcers contained granular remains of eosinophils and/or basophils. The purulent exudate that covered the walls and base of the ulcers contained abundant trophozoites de *E. histolytica*, located principally at the edges of the ulcers and rarely in the blood vessels. In 50% of the cases *E. histolytica* trophozoites were observed in the pericolic fatty tissue, but not in the adjacent ischemic mucosa.

A few years later a report was published about 55 patients with FAC (Takahashi et al., 1997) treated in the Hospital de la Nutrición Salvador Zubirán in Mexico City (1943 to 1994).
operative mortality was 76% and the total mortality 89%, both associated mainly with a reduced level of leukocytes. Furthermore, 54% were found to have an association with amebic liver abscess (AHA), and the most common systemic illness was Diabetes Mellitus. Macroscopically the colon was observed to have multiple sites of perforation, with amebic appendicitis found in 5 cases and ameboma in 4 others. Microscopic analysis showed necrosis and the presence of *E. histolytica* in the upper and lower layers of the colon, with acute and/or chronic inflammation in the external muscular layer. Cases of FAC are uncommon, but the majority result in death of the patient. To the naked eye, the colon presents a great quantity of ulcers with robust necrosis and mucosa exudate, but surrounded by apparently normal tissue. The ulcers contain round or oblong *E. histolytica* (with erythrocytes and phagocytes) the size similarly to macrophages.

Recently associations have been reported between FAC and other pathologies such as tuberculosis (Park et al., 2000), co-infection with *Actinomyces* (Nishena et al., 2009) and *Histoplasmosis* (Koh et al., 2010). One case was published of FAC associated with a chemotherapy treatment for advanced gastric cancer (Hanaoka et al., 2009). What stands out from these reports is the association of FAC with a deficit in the immune system and malnutrition, which further emphasizes the need to analyze the role of the distinct cells of the immune response against the *E. histolytica*, and especially whether there is an active inflammatory response.

Fig. 2. **Histology of a healthy human colon.** The mucosa (M), epithelial tissue (E) and Lieberkhün crypts (LC), surrounded by the lamina propria (LP) and delimited by the *muscularis mucosae* (mm) from the submucosa (SM), which contains lymphatic nodes (LN). The external muscular tissue (EM) and serous tissue (H & E; X25).
3.1 The host-parasite interaction during FAC

Before describing the structure of the colon with amebiasis, the histological structure of a healthy colon must first be laid out.

The Ventura-Juárez group described (2007), in mucosa (M) and submucosa (SM) of healthy colon, the location of cells of the innate and adaptive immune response, by using histochemical and immunohistochemical techniques, finding macrophages, NK cells, eosinophils, mast cells, CD4 and CD8 lymphocytes, but without neutrophils (Fig 3 a-f). Additionally, abundant IgA, IgG and IgM producing cells were found (Fig 3 g-i), which had been previously described by Douglas & Rodger (1997).

Fig. 3. Cells from the innate and adaptive immune response in healthy human colon. Cells from the innate (a-d) and adaptive (e-i) immune response located in the lamina propria and submucosa of healthy human colon tissue. (Histochemistry and Immunohistochemistry X400). (Ventura-Juárez et al., 2007).

3.2 Histopathology of amebic ulcers in fulminant amebic colitis

In order to describe the role of the immune response and inflammation during FAC, eleven tissue samples were analyzed (from 5 women and 6 men), originating from patients who underwent surgery of the ileum and colon during the period of 1999 to 2004 in three hospitals in Mexico (Ventura-Juárez et al., 2007). Macroscopic analysis of intestines with FAC showed, externally, intestinal perforations (arrows) with hemorrhagic necrosis
(asterisk) (Fig. 4a), and internally, ample zones of necrosis with bloody-mucosa deposits (asterisk) and thickening of the mucosa with perforations (arrows) (Fig. 4b).

Fig. 4. **Macroscopic characteristics of fulminant amebic colitis:** (a) External view of the colon, where large areas of hemorrhagic necrosis (*) and perforations can be appreciated (arrows); small normal-looking areas of the colon and the mesentery (**). (b) Internal view of the colon, where hemorrhagic necrosis and fibrinoid deposits are observed (*), along with amebic ulcers (arrows).

The amebic ulcer (Fig. 5) is characterized by the classic form of the “flask ulcer” delimited (blue line) laterally by Mucosa (M), Submucosa (SM), external muscular tissue (EM) and the peritoneum (P). The ulcer, viewed from the intestinal lumen (IL) toward the deep ulcer (DU), shows: 1) a thickened surface zone composed of lytic material mixed with mucous, (**) 2) a thickened intermediate zone with abundant proteinaceous material (PM), and 3) a deeper zone with the mucosa and submucosa damaged by the amebic invasion and an area where the mucosa and submucosa are fused together, which is termed the necrotic zone. At the center of this zone there is an area of discontinuity of the external muscular tissue and peritoneum, where the intestinal perforation is formed (arrow).

Histological cuts show *E. histolytica* located abundantly in the mucosa outside (Fig. 6a) and inside the amebic ulcer, mixed with cells of the inflammatory infiltrate. In the external muscular layer (EM) of the ulcer, abundant *E. histolytica* trophozoites were found, although
Fig. 5. Amebic ulcer characteristic of FAC. The amebic ulcer (dotted line) is delimited by the mucosa (M), submucosa (SM), external muscular tissue (EM) and the peritoneum (P). The ulcer consists of: (1) a surface zone formed by mucous (**), 2) an intermediate zone with proteinaceous material (PM), and 3) a deep zone that contains damaged mucosa (M) and submucosa (SM) and a necrotic zone (NZ). At the bottom of the ulcer is found a zone of discontinuity of the external muscular (EM) and the peritoneum (P), where the intestinal perforations are formed (arrow). View from the intestinal lumen (IL) and the deep ulcer (DU).

without inflammatory infiltrate, that caused the intestinal perforation (Fig. 6b). Curiously, *E. histolytica* trophozoites were observed on the edge of the ulcers or within them, even when these areas extended to the entire mucosa-submucosa with necrotic material, cellular debris and strands of fibrins. Nevertheless, inside some dilated blood vessels (bv) *E. histolytica* can indeed be observed (Fig. 6c).

4. Role of the cellular immune response

The mechanisms of damage caused by the *E. histolytica* in the mucosa of the colon of FAC patients are similar to those described in liver with invasive amebiasis (Aikat, 1979; Ventura-Juárez, 1997). It has been seen that when *E. histolytica* are present, tissue damage can be caused by *E. histolytica* adhesion, lysis of host cells, and effects of the proteolytic enzymes derived from the parasite (Huston, 2004; Stanley & Reed, 2001). However, when *E. histolytica* are not present in the tissue, damage probably arises from an ischemia or the immune response of the host (Campos-Rodríguez et al., 2009; Stanley & Reed, 2001).
4.1 In FAC, the cellular immune response does not participate in the death of *E. histolytica* trophozoites

Neutrophils and macrophages are important effector cells in the defense of the host against *E. histolytica* (Cantellano & Martínez-Palomo, 2000; Ghadirian & Denis, 1992; Seydel et al., 1997; Tsutsumi et al., 1984; Velázquez et al., 1998). Ventura-Juárez et al (2007) demonstrated that during an amebic invasion, the inflammatory response is restricted to the areas without cellular damage. That is, the fact that neutrophils are abundant in the mucosa adjoining the ulcer (20.7272 ± 7.2950), absent in the zones distant from the ulcer, and are scarce and rarely in contact with the trophozoites in lytic zones of the ulcer that contain *E. histolytica* (7.2950 ± 4.6363) (Fig. 7 a, b, e), indicates that the amebic invasion does not prompt a generalized inflammatory response.

Macrophages, on the other hand, are scant in the amebic ulcer compared with a healthy intestine (56.8 ± 14.6697), and are principally in the lamina propria. They were found to be greatly diminished in the mucosa inside of the ulcer (1.7272 ± 1.4893) compared to mucosa outside (9.1818 ± 1.3280) (Fig. 7 c-e). This scarcity of macrophages in the amebic ulcer could be caused by their reduced migration as a consequence of the secretion of the locomotion inhibitory factor of monocytes (MLIF) (Kretschmer et al., 1985).

The fact that neutrophils and macrophages were not found in direct contact with *E. histolytica* (Fig. 7b, d) leads to the conclusion that these cells probably do not participate in the death of *E. histolytica* trophozoites, as this process is apparently dependent on direct contact (Burchard et al., 1993; Martinez-Palomo, 1987; Petri et al., 2002). Nevertheless, neutrophils and macrophages could be participating in the destruction of colonic tissue, as has been suggested by various researchers (Pittman, 1976; Tsutsumi et al., 1990; Tsutsumi et al., 2006) and confirmed by experiments conducted in animal models (Rivero-Nava 2002; Stanley & Reed 2001), in which it has been demonstrated that mucosa of healthy colon (without inflammation) do not present neutrophils (Lee et al., 1988).
Fig. 7. Distribution of neutrophils and macrophages in the intestine of patients with FAC. 
(a) Abundant neutrophils (CD15+; arrows) in mucosa adjoining the amebic ulcer. (b) 
Trophozoites (*) surrounded by cells without any contact with neutrophils (CD15+; arrows) 
in a necrotic zone of the ulcer. (c) Macrophages (CD68+; arrows) in lamina propria outside 
of the ulcer. (d) Macrophages (arrows; CD68+) without contact with trophozoites (*). All 
photos were taken with a magnification of X400. (e) Graphic representation of the number of 
neutrophils (PMN) and macrophages (Mac) in healthy intestine, as well as areas outside 
(OAU) and inside (IAU) the ulcer of intestine with FAC. The bars represent the mean ± SD 
(p< 0.05; Students t Test).

Similarly, in the tissue of patients with FAC, a greater quantity of NK cells (CD57) were 
found than in healthy tissue (2.8 ± 0.8366). These cells in lamina propria outside the ulcer 
(5.6363 ± 1.8586) were abundant and were mixed with cellular debris. Inside the ulcer NK 
cells were less abundant (1.5454 ±1.0357) and had no contact with E. histolytica trophozoites, 
suggesting that they are not responsible for the elimination of the parasite (Fig. 8a y d). In an 
animal model of AHA in mice, it has also been observed that NK cells are not found in the 
inflammatory infiltrate or in cells that delimit the lesion (Jarillo-Luna, 2002). However, 
another study reported that NK cells activated by lipopeptidophosphoglicane from E. 
histolytica reduce the size of AHA (Lotter et al., 2009).
Fig. 8. NK cells, eosinophils and mast cells are scarce in ulcers in the intestine of patients with FAC. (a) NK cells (arrows) are distant from the trophozoites in the lamina propria (Immunoperoxidase, X400). (b) Eosinophils (arrows) are observed in the lamina propria outside of the ulcer remote from trophozoites (Histochemistry, X400). (c) Mast cells (arrows) in the lamina propria outside the ulcer, distant from trophozoites (Histochemistry, X400). (d) Graphic representation of the number of NK cells (NK), eosinophils (Eos) and mast cells (Mast) in healthy intestine, as well as in areas outside (OAU) and inside (IAU) the ulcer in the intestine of patients with FAC. Bars represent the mean ± SD (p< 0.05; Students t Test).

Moreover, eosinophils and mast cells are also implicated in the cellular response and have been found to be involved in the reduction of amebic damage in various in vivo models (Houpt, 2002; Jarillo-Luna, 2002; López-Osuna et al., 1997, 2002). By using histochemical techniques in human intestinal tissue with FAC, eosinophils were stained with eritrosine B 1.5% (Benítez et al., 1987) and mast cells with toluidine blue 0.7% (Enerback, 1986; Ventura-Juárez et al., 1990). Then, by using light microscopy, it was observed that both types of cells diminished significantly in the lamina propria and inside the ulcer with respect to healthy intestine (9.4 ±3.435; 8.0 ± 2.9154), suggesting that E. histolytica could participate in the destruction of these cells (Fig. 8d).

Eosinophils are located mostly in the lamina propria outside of the ulcer (6.5454 ± 1.5724) and only scanty (3.0909 ± 0.94387) in the lamina propria of the amebic ulcer (Fig. 8b y d). It has been shown by in vitro studies that the MLIF produced by E. histolytica do not affect the
locomotion and respiratory burst of human eosinophils (Rico & Kretschmer, 1997). However, *E. histolytica* is capable of destroying normal eosinophils (not activated) (López-Osuna & Kretschmer, 1989).

Mast cells did not show significant changes between the lamina propria inside (2.0000 ± 1.1832) and outside (1.6124 ± 0.00009) the amebic ulcer (Fig. 8c y d). Some studies reveal that there is an association between the activity of mast cells and the deterioration of immunity. In mice infected by nematodes, mast cells and their proteases, specifically protease-1, increased the elimination of the parasite (Knight et al., 2000), possibly through increasing vascular permeability and epithelial permeability. Taking this into account, and considering that *E. histolytica* trophozoites favor zones of epithelial rupture, *E. histolytica* could be benefited by the permeability of the epithelial cells. Moreover, mast cells also could be a direct cause of proteases or proinflammatory cytokines, or perhaps through neutrophils dependent on IgE and the recruitment of monocytes (Wershil et al., 1996). In a model of amebic colitis in mice, it has been determined that mast cells do not protect against amebiasis (Houpt et al., 2002).

<table>
<thead>
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<th>Cell type</th>
<th>Function in intestinal immunity</th>
<th>Healthy intestine</th>
<th>Intestine in patients with FAC</th>
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<td>Inside the amebic ulcer</td>
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<tr>
<td></td>
<td></td>
<td>E</td>
<td>LP</td>
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<td>PMN</td>
<td>First phagocytic cells attracted to the damaged site and inhibited by <em>E. histolytica</em>.</td>
<td>3.1510</td>
<td>20.727*</td>
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<td>Mac</td>
<td>Phagocytic cell that presents antigens destroyed by <em>E. histolytica</em>.</td>
<td>56.800</td>
<td>9.1818*</td>
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<td>NK</td>
<td>Cells responsible for activating macrophages and liberating IFN gamma, attracted to the damaged site and destroyed by <em>E. histolytica</em>.</td>
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<td>5.6363**</td>
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<td>Eos</td>
<td>Cells with anti-helminthic activity that are nevertheless inhibited by <em>E. histolytica</em>.</td>
<td>9.4000</td>
<td>6.5454*</td>
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<td>Cytotoxic cells inhibited by <em>E. histolytica</em> in necrotic zones of the ulcer.</td>
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</tbody>
</table>

Table 2. Role of the Cellular Immune Response during fulminant amebic colitis. Neutrophils (PMN), Macrophages (Mac), NK cells (NK), Eosinophils (Eos), Mast cell (Mast). *Significant values with respect to healthy intestinal tissue. # Significant values with respect to areas outside the ulcer of the intestine of patients with FAC.
In general, there were a lesser number of immune cells in areas inside the amebic ulcer than areas outside (see table 2). Various explanations could be given for this fact: (a) the immune cells are eliminated by products of *E. histolytica*; (b) migration of cells is inhibited by the locomotion inhibitory factor of monocytes, (c) the dysfunction of endothelial cells is induced by *E. histolytica*, which causes thrombosis and local ischemia, and consequently a reduced cellular migration (Campos-Rodríguez et al., 2009).

### 4.2 In FAC, *Entamoeba histolytica* inhibits the cytotoxic response of CD8 lymphocytes

By observing intestinal tissue of patients with FAC, descriptions have been made not only of the cells and molecules of the innate immune response, but also the cells of the acquired cellular immune response (T CD4+ lymphocytes, T CD8+ lymphocytes). These latter cells require at least two weeks to be able to differentiate and recognize antigens. No significant changes were found between the number of CD4+ lymphocytes of the lamina propria of healthy mucosa (4.3441 ± 1.1639), and the number of these cells in patients with FAC inside (4.8112 ± 0.8556) and outside (3.6531 ± 0.9011) the lamina propria of the intestine (Figs. 9a and 9c).

![Decrease of T CD8+ cells in amebic ulcers](image)

**Fig. 9. Decrease of T CD8+ cells in amebic ulcers.** (a) T CD4+ cells located in the lamina propria of the amebic ulcer. (b) Scarce T CD8+ lymphocytes in the lamina propria of the amebic ulcer (Immunoperoxidase, X400). (c) Graphic representation of CD4+ and CD8+ lymphocytes in healthy intestine, as well as areas outside (OAU) and inside (IAU) the ulcer in the intestine of patients with FAC. Bars represent the mean ± SEM (*p* ≤ 0.05; Tukey Test).

These results suggest that the amebic invasion does not alter the activation of these T CD4+ cells. Moreover, there were no significant changes in the number of CD8+ cells of the lamina propria between healthy intestine (6.7001 ± 1.3101) and areas outside of the ulcer (6.6 ± 1.1), although a diminished recruitment of these cells was observed in the lamina propria of amebic ulcers (2.1411 ± 0.9111)(Figs. 9b and 9c).
The role of T CD4+ and CD8+ cells in intestinal amebiasis is unknown, although it has been proposed that T CD8+ cells are involved in the lysis by direct contact of *E. histolytica* (Martínez-Palomo, 1987). If so, the low number of T CD8+ lymphocytes given by the Th2 response could contribute to the persistence of amebas in the colonic mucosa (see table 2) (Ventura-Juárez et al., 2007).

5. Role of the humoral immune response

In the colon, immunoglobins (Igs) are in part responsible for maintaining equilibrium between the host and parasite. In the intestine the first immunoglobulin to express itself, IgA, prevents microorganisms from penetrating the mucosa due to its anti-adherence properties. If the invasion succeeds in spite of this defense, IgG is produced and IgM begins to form binding complexes with the complement.

Ventura-Juárez (2007) studied intestine in patients with FAC and healthy human intestine by immunohistochemical techniques in order to localize the immunoglobulins IgA, IgG and IgM, finding plasma cells IgA, IgG and IgM (Fig. 10) in the lamina propria outside and inside the amebic ulcer.

The number of cells positive for IgA and IgG in lamina propria outside the ulcer was significantly greater (38.5454 ± 4.8859, 40.0000 ± 7.2938) with respect to lamina propria inside the ulcer (4.8181 ± 1.6011; 1.7272 ± 1.42062) and in healthy intestine (22.0000 ± 4.3588; 4.8000 ± 0.8366) (Fig. 10a-d, g). However, both types of plasma cells significantly diminished in the lamina propria of the amebic ulcer with respect to healthy intestine.

In contrast, IgM plasma cells significantly diminished in the lamina propria of the amebic ulcer with respect to healthy intestine (29.6666 ± 2.5166). That is, in the lamina propria outside the ulcer (6.0909 ± 1.9211) there is a significantly greater number of IgM cells with respect to the ulcer (2.9090 ± 1.0444) (Fig. 10e-g). Additionally, no inflammatory cells were found in contact with trophozoites, meaning that they probably do not participate in resolving the amebic invasion. Indeed, these cells could contribute to tissue damage.

Plasma cells can be involved in the synthesis of antibodies against amebic antigens. About 64% of patients with amebic colitis have an increase in the titers of antibodies for *E. histolytica*, which are used in the diagnosis of the amebic invasion.

However, these antibodies do not protect against the pathogen. IgA is a central component of the immune defense, modulating the host-parasite interaction. It is the dominant immunoglobulin of the intestinal surface (see table 3). It has been seen that the cysteine proteases of *E. histolytica* break down IgA and IgG. Broken down IgG, in turn, reduces the affinity of antibodies for antigens. If the Fc portion is removed, the trophozoites could evade the immune response byencasing themselves in immunogenic surface molecules found in Fab fragments. This could prevent the activation of the complement by the classic pathway and attack the immune cells with the anchor corresponding to the Fc receptor. Thus, the parasite could move around the internal medium, ignoring the immune system of the host (Mortimer & Chadee, 2010).
Fig. 10. **Distribution of plasma cells in intestines with FAC.** (a) Abundant IgA+ cells (arrows) are found in the lamina propria outside the ulcer. (b) Scarce IgA+ cells (arrows) in the lamina propria near the trophozoites (*) of the amebic ulcer. (c) Numerous IgG+ cells (arrows) are found en la lamina propria nearly the ulcer, close to the necrotic zone. (d) Scant IgG+ cells (arrows) in the lamina propria around the trophozoites (*). (e) Scarce IgM cells (arrows) in the lamina propria outside the amebic ulcer. (f) IgM+ cells in the lamina propria of the ulcer near trophozoites (*). (Immunoperoxidase, X400). (g) Graphic representation of the number of IgA+, IgG+ and IgM+ in healthy intestine, as well as areas outside (OAU) and inside (IAU) the ulcer of the intestine of patients with FAC. Bars represents the mean ± SD (p< 0.05; Student t Test).
Fulminant Amoebic Colitis: Role of the Innate and Adaptive Immune Responses

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Function in intestinal immunity</th>
<th>Healthy intestine</th>
<th>Intestine in patients with FAC</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>E</td>
<td>LP</td>
</tr>
<tr>
<td>IgA</td>
<td>Principal Immunoglobulin of defense in the mucosa. Abundant during the processes of FAC, and destroyed by <em>E. histolytica</em>.</td>
<td>22.0000</td>
<td>38.5454*</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin responsible for activating the complement. Abundant during the processes of FAC.</td>
<td>4.8000</td>
<td>40.0000*</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin of defense in the mucosa. Its production is inhibited by <em>E. histolytica</em>.</td>
<td>29.6666</td>
<td>6.0909*</td>
</tr>
</tbody>
</table>

Table 3. Role of the Humoral Immune Response during fulminant amebic colitis. *Epithelium (E), Lamina propria (LP), Sub-mucosa (SM).* Significant values with respect to healthy intestinal tissue. # Significant values with respect to areas outside the ulcer of the intestine of patients with FAC.

6. Role of anti-inflammatory and pro-inflammatory cytokines in FAC

The role of the acquired cellular immune response in protecting against fulminant colitis has not yet been well defined. It is still not clear if the type 1 (Th1) or type 2 response (Th2) dominates the immune response in amebic colitis. Information is lacking in data from the literature about cytokine expression in the colon of patients with amebic colitis. According to results obtained from human intestine with FAC by the Sierra-Puente et al (2009), both pro-inflammatory cytokines (IL-8 e INFγ) and anti-inflammatory cytokines (IL-4, IL-10, TGF-β) were found, promoters of the Th1 and Th2 type response, respectively (Guo et al, 2008; Sierra-Puente et al., 2009).

6.1 In FAC, epithelial cells of the intestine produce IL-8

*In vitro* studies have demonstrated that *E. histolytica* stimulates the production of IL-8, a pro-inflammatory chemotactic cytokine for neutrophils (Yu & Chadee, 1997). Also using antibodies against human IL-8, cells positive to this cytokine were identified in the epithelial cells outside the ulcer from patients with FAC (2.200 ± 0.4667), while no cells positive to this cytokine were found in healthy intestine (Fig. 11a) (Sierra-Puente et al., 2009). In the model of SCID mice with intestinal xenografts from humans infected with virulent *E. histolytica* trophozoites, IL-8 was detected in epithelial cells distal of the ulcer (Seydel et al., 1997), which corroborates the findings by our workgroup.

In a previous study, Ventura-Juárez (2007) demonstrated that in human intestine with FAC, the mucosa adjoining the amebic ulcer presented a great quantity of neutrophils, which are related with IL-8 produced by epithelial cells located in the same area of the intestine. Some researchers support the hypothesis that the high production of IL-1 and IL-8 by epithelial cells could be a key contributor to the pathogenesis of amebic infection. This probably takes place through the attraction of neutrophils, which in turn increases inflammation and damage (see table 4) (Garcia-Zepeda et al., 2007; Seydel et al., 1997).
Fig. 11. *E. histolytica* induces the overproduction of IL-8 by epithelial cells. (a) IL-8+ epithelial cells outside the amebic ulcer (arrows) (Immunoperoxidase, X400). (b) Graphic representation of IL-8+ epithelial cells from healthy intestine and outside the ulcer in the intestine of patients with FAC. Bars represents the mean ± SEM (p ≤ 0.004; Students t Test).

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E</td>
<td>LP</td>
</tr>
<tr>
<td>IL-8</td>
<td>Cytokine that attracts and activates neutrophils. Cytokine produced in processes of FAC.</td>
<td>0</td>
<td>2.200*</td>
</tr>
<tr>
<td>IL-10</td>
<td>Stimulates the synthesis of IgA, antagonizes Th1 cells. Cytokine produced in processes of FAC.</td>
<td>2.3002</td>
<td>10.351*</td>
</tr>
<tr>
<td>IL-4</td>
<td>Cytokine that promotes the development of B cells producing IgA and IgG. Cytokine produced in processes of FAC.</td>
<td>1.0001</td>
<td>12.3600*</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Cytokine that inhibits Th1 cells. TGF-beta-producing cells inhibited in the processes of FAC.</td>
<td>13.4100</td>
<td>5.0290</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Cytokine that activates the immune response. There is no production of IFN gamma in the process of FAC.</td>
<td>Few</td>
<td>Few</td>
</tr>
</tbody>
</table>

Table 4. Role of the cytokines during fulminant amebic colitis. *Epithelium (E), Lamina propria (LM), Sub-mucosa (SM).* * Significant values with respect to healthy intestinal tissue. # Significant values with respect to areas outside the ulcer of the intestine of patients with FAC.
6.2 During FAC, the anti-inflammatory response is augmented, and thus the prevalence of a Th2 type response

IL-10, a cytokine of the Th2 response with pleiotropic functions, has immunosuppressive properties and acts in various immunological settings. The augmenting of this cytokine in amebiasis is probably responsible for enabling ample amebic invasion of intestine as well as liver (Bansal et al., 2005; Sierra-Puente et al., 2009). Sierra-Puente et al (2009) were the first to publish that IL-10 is produced by epithelial cells in the intestine of patients with FAC. By using antibodies from rabbit anti-human IL-10, it was observed in intestinal tissue of patients with FAC that this cytokine was intensely expressed by epithelial cells outside the ulcer (10.3512 ± 1.9220) (Fig. 12a) compared to healthy intestine (2.3002 ± 0.5814). On the other hand, in lymphoid cells of the lamina propria infected by *E. histolytica*, there was no positive reaction to this cytokine (Fig. 12b).

![Fig. 12. Increase of IL-10 in epithelial cells during FAC. (a) Epithelial cells positive to IL-10 (arrows) outside the amebic ulcer (Immunoperoxidase, X400). (b) Graphic representation of IL-10+ cells in healthy intestines and outside the ulcer (OAU) in the intestine of patients with FAC. Bars represents the mean ± SEM (p ≤ 0.01; Students t Test).](image)

In different experimental models, an important role has been suggested for IL-10 in the stimulation of innate resistance to *E. histolytica* infection, although the possible mechanisms are still unknown (Hamano et al., 2006). One possible mechanism could be the participation of IL-10 in the stimulation of the production of mucous by goblet cells in the epithelium (Schwerbrock et al., 2004), which in turn maintains the protective mucous barrier. Another possible mechanism is based on the immunosuppressive effects of IL-10 from epithelial cells on leukocytes (García-Zepeda et al., 2007). Reports in the literature indicate that patients with invasive amebiasis (colitis and AHA) have a greater expression of IL-10 by mononuclear cells of peripheral blood (Bansal et al., 2005).

IL-4 is another cytokine classically generated by Th2 lymphocytes whose principal function is to induce a humoral response. In patients with amebiasis, this cytokine probably is
responsible for suppressing the IFN-γ producing Th1 cells, and in this way contributing to the resistance to amebic invasion (Guo et al., 2008). Sierra Puente et al (2009) found, by employing specific antibodies, that IL-4 is expressed in numerous lymphocytes located in the lamina propria adjoining the amebic ulcer (12.3600 ± 1.6660) (Fig. 13a-b). No positive reaction to this cytokine was found in lymphocytes located in the ulcer near trophozoites (figure 13a), although there were traces found in lymphocytes from healthy intestines (1.0001 ± 0.4082) (Fig. 13b).

In peripheral blood of individuals infected with E. histolytica, it has been demonstrated that mononuclear cells express IL-4 to a significantly greater degree than healthy individuals (Sánchez-Gillén et al., 2002). Furthermore, in a study on a cecal loop mice model of amebiasis, a rapid and sustained increase was shown in the cytokines type Th2 (IL-4 +, IL-5 +, IL-13+) as well as an inhibition of the production of IFN-γ (Guo & Houpt, 2008).

It is well-known that the immunoregulation phenomenon in the intestine is mainly driven by TGF-β producing Th3 cells, which also have regulating functions for the inflammatory response (Houpt et al., 2002).

Sierra-Puente et al (2009) identified TGF-β producing cells with mouse anti-human TGF-β antibodies (Fig. 14a), noting a significant diminishment of positive epithelial cells in patients with FAC (7.7880 ± 1.1410) with respect to the epithelium of healthy intestinal tissue (13.4100 ± 1.1400). However, no significant difference was found in the lamina propria of intestines of patients with FAC (7.4740 ± 1.2740) compared to samples from healthy intestinal tissue (5.0290 ± 1.3030) (Fig. 14b). The decrease in TGF-β producing epithelial cells in intestines with FAC perhaps owes itself to the fact that the presence of E. histolytica causes the loss of immunological homeostasis in the intestinal lumen and mucosa. In patients with FAC, the presence of E. histolytica trophozoites induces a decrease in TGF-β production in the epithelium of the mucosa and an increase in the synthesis of IL-1 and IL-8, which are chemotactic and pro-inflammatory cytokines (Houpt et al., 2002; Sierra-Puente et al., 2009).

IFN-γ plays an important role in the pathogenesis of amebiasis in patients, rodent models and in vitro experiments. In general, in humans with amebiasis (Sierra-Puente et al., 2009) and in
Fulminant Amoebic Colitis: Role of the Innate and Adaptive Immune Responses

Fig. 14. TGF-ǃ-producing cells of the mucosa in intestines of patients with FAC. (a) Epithelial cells positive to TGF-ǃ (arrows) were detected in the Lieberkhün crypts (LC) and the lamina propria (LP) (Immunoperoxidase, X400). (b) Graphic representation of TGF-ǃ - cells located in epithelium of the Lieberkhün crypts (LC) and the lamina propria (LP) of healthy intestinal tissue and areas outside of the ulcer in the intestine of patients with FAC. Bars represents the mean ± SEM (p ≤ 0.01; Students t Test).

In studies conducted in the intestine of patients with FAC, Sierra-Puente (2009) did not find IFN-ǃ expression in inflammatory cells, coinciding with the finding of scarce macrophages in amebic ulcers reported by Ventura-Juárez (2007). Hence, the amoebicidal factor mediated by IFN-ǃ is inhibited in the intestine, a phenomenon probably related to the increase in the production of IL-4 and IL-10, which in turn principally inhibit IFN-ǃ producing Th1 cells (Sierra-Puente et al., 2009). It is worth noting that IFN-ǃ was not expressed in inflammatory infiltrate cells, whether near to or distant from amebas, but was indeed detected in the majority of *E. histolytica* trophozoites (Fig. 15) (see table 4). The positive reaction of trophozoites to IFN-ǃ could be due to the presence of T cells phagocytized by amebas.

7. CD59 could be linked to *E. histolytica* resistance to the innate immune response

It can be seen that during the processes of FAC, the activity of the cellular and humoral immune response (Ig) is inhibited in necrotic zones of ulcers. On the other hand, in areas outside the amebic ulcer and in absence of trophozoites, the cellular response and IgA and IgG producing plasma cells are active. This leads to the conclusion that *E. histolytica* possibly has some component on its membrane that allows it to protect itself from the immune response, and thus proceed to damage the intestine.
CD59 is a widely distributed membrane glycoprotein weighing 18-20 kDa. It covalently binds the membrane of the trophozoites to the surface of a host cell through an anchor called phosphatidil inositol. CD59 inhibits the cytolytic activity of the complement by binding to C8 and C9, and thus blocking the formation of the complex that could attack the membrane of the trophozoites (Lachmann, 1991).

Previous studies with pathogenic *E. histolytica* trophozoites have demonstrated the presence of proteins that share epitopes with human CD59, which probably protects amebas against lysis by the complement (Braga et al., 1992; Flores-Romo et al., 1994; Petri et al., 2002; Fritzinger et al., 2006). Nevertheless, the group of Ventura-Juárez (2009) found the antigen of CD59 by using immunohistochemical and immune-gold techniques. By light microscopy they observed that all trophozoites of *E. histolytica* immunostained with the CD59 antibody existed individually in necrotic zones of the amebic ulcer in the presence or absence of inflammatory infiltrate (Fig. 16a). By Electron Transmission Microscopy, trophozoites CD59 immunostained were identified, principally on their cellular membrane and to a lesser extent in the cytoplasm and vacuoles (Fig. 16b). However, *in vitro* it was observed that only
some trophozoites express the CD59 protein (Fig. 16c), suggesting that only the trophozoites positive to CD59 manage to evade the immune response and thus induce cellular damage in the intestine.

Fig. 16. *E. histolytica* trophozoites present CD59+ on their membrane during FAC. (a) In human intestines with FAC, CD59 is found on the plasmatic membrane of whole trophozoites (arrow), surrounded by a halo without tissue or cellular debris (*) (Immunoperoxidase, X400). (b) Trophozoite marked with CD59+ presents abundant immunostaining on the cell membrane (arrow) and to a lesser extent on the cytoplasm (double arrows) located in the intestine of patients with FAC (Immune-gold, Electron Transmission Microscopy, X9450). (c) Some *E. histolytica* trophozoites in vitro present positive immunoreaction to CD59 on the plasmatic membrane (Immunoperoxidase, X1000).

On the other hand, on extract proteins of *E. histolytica* trophozoites, it was confirmed by Western Blot that the protein located on the surface of trophozoites corresponds to a molecular weight of approximately 21 kDa, similar to CD59 of mammalian cells (18–20 kDa) (Davies & Lachmann, 1993) as well as to the CD59 protein on *N. fowleri* (Fritzinger et al., 2006). In spite of this information, the source of these CD59 molecules in intestines with FAC is not clear. The presence of immunoreactive material in cytoplasm and vacuoles could indicate an endogenous synthesis. Another possibility is that CD59 recaptures intestinal fluid or phagocytes erythrocytes (Gutierrez-Kobeh et al., 1997). Therefore, the CD59 protein on the surface of *E. histolytica* trophozoites that invade human colon probably have an important mechanism of protection against the action of macrophages that enable their pathogenic mechanism to later do damage (Ventura-Juárez et al., 2009).

So far the precise mechanisms that allow *E. histolytica* to invade the intestine and cause peritonitis have not been clearly identified. However, it is known that there is no production of INFγ and IgM is decreased in intestinal tissue, which indicates the importance of determining these two immunological parameters in the serum of patients.

8. Conclusion

Although fulminant amebic colitis affects a tiny number of patients, it is a mortal manifestation of invasive intestinal amebiasis, and is generally associated with other pathologies. *E. histolytica* induces the activation of the innate immune response, which is not
capable of eliminating the parasite, but is indeed capable of contributing to the pathogenesis by causing cellular damage on the walls of the colon. At the same time, *E. histolytica* partially induces an adaptive immune response that has immunosuppressive features. Much remains to be elucidated, as there is still no model that enables researchers to reproduce all of the aspects of the host-parasite interaction taking place in humans.

9. Acknowledgments

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10. References


Fulminant Amoebic Colitis: Role of the Innate and Adaptive Immune Responses


Inflammation of the colon is collectively called "Colitis". Since a variety of conditions may cause colitis and its manifestations are similar among the causes, selection of the right treatment based on the correct diagnosis is important in the management of this group of illnesses. Over the last few decades, a major shift has been observed in the clinical attention to the pathogenesis of colitis from infectious to idiopathic inflammatory bowel diseases. Colitis cases that are associated with chemical therapeutics and specific pathogens such as amoeba, have become prominent in hospitalized individuals and immune deficient patients, respectively. In addition, a great deal of progress has been made in colitis research triggering the need for updating our knowledge about colitis. This book Colitis provides comprehensive information on the pathogenesis, mechanism of resolution, and treatment strategies of colitis.

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