Pathogenesis of infection by *Entamoeba histolytica*

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Abstract. *Entamoeba histolytica*, a protozoan parasite, is the etiologic agent of amoebiasis in humans. It exists in two forms—the trophozoite which is the active, dividing form, and the cyst which is dormant and can survive for prolonged periods outside the host. In most infected individuals the trophozoites exist as commensals. In a small percentage of infections, the trophozoites become invasive and penetrate the intestinal mucosa, causing ulcers. The trophozoites may reach other parts of the body—mainly liver, where they cause tissue necrosis, leading to life-threatening abscesses. It is thought that pathogenesis of infection by *Entamoeba histolytica* is governed at several levels, chief among them are (i) adherence of trophozoite to the target cell, (ii) lysis of target cell, and (iii) phagocytosis of target cell. Several molecules which may be involved in these processes have been identified. A lectin inhibitable by galactose and N-acetyl-D-galactosamine is present on the trophozoite surface. This is implicated in adherence of trophozoite to the target cell. Various amoebic pore-forming proteins are known, of which 5kDa protein (amoebapore) has been extensively studied. These can insert into the lipid bilayers of target cells, forming ion-channels. The phagocytic potential of trophozoites is directly linked to virulence as measured in animal models. Factors like association of bacteria with trophozoites also influence virulence. Thus, pathogenesis is determined by multiple factors and a unifying picture taking into account the relative contributions of each factor is sought. Recent technical advances, which includes the development of a transfection system to introduce genes into trophozoites, should help to understand the mechanism of pathogenesis in amoebiasis.

Keywords. *Entamoeba histolytica*; pathogenesis; amoebiasis.

1. Introduction

The protozoan parasite, *Entamoeba histolytica*, is the causative agent of amoebiasis in humans. According to the best estimates (Walsh 1986) approximately 48 million individuals suffer from amoebiasis throughout the world. In 1984, at least 40,000 deaths were attributed to amoebiasis. Amoebiasis is a major problem in developing countries such as India. This is primarily because of inadequate sanitation and contaminated food and drinking water.

Pathogenesis of amoebiasis is believed to be a multistep, multifactorial process. Though a large number of studies have attempted to unravel the factors/molecules responsible for the pathogenesis of amoebiasis, the processes involved in pathogenesis are by no means well understood. The aspects of pathogenesis which have been investigated experimentally can be broadly categorized into mechanisms involving (i) interactions with the intestinal flora, (ii) lysis of target cell by direct adherence, (iii) lysis of target cell by release of toxins and (iv) phagocytosis of target cells. Each of
these will be discussed after a brief description of the life cycle of *E. histolytica* and pathology of amoebiasis.

2. **Life cycle of *E. histolytica***

The organism exists in two forms—the trophozoite or the dividing form and the cyst which is the dormant form. Human infection usually begins with the ingestion of the cyst which is present in food and/or water contaminated with human fecal material. Cysts survive the acidic pH of the stomach and pass into the intestine. In the ileo-cecal region, cysts undergo excystment and each cyst gives rise to eight trophozoites. These migrate to and multiply in the colon. In most cases, trophozoites in the intestine live as commensals. Occasionally, however, trophozoites attack and invade the intestinal mucosa causing dysentery and/or progress through the blood vessels to extra-intestinal locations like liver, brain and lungs, where they may form life-threatening abscesses. In the intestine, many of the trophozoites encyst and produce quadrinucleated cysts. Both trophozoites and cysts are excreted along with the feces. Cysts can survive for prolonged periods outside the host while the trophozoites survive only for a few hours. Trophozoites play no role in transmission of the disease but are responsible for producing tissue pathology. The reservoir of human infection is the "carrier" or asymptomatic human host who continuously passes cysts.

3. **Pathology**

Amoebic infection of the human intestine ranges in spectrum from luminal colonization to mucosal invasion (Joyce and Ravdin 1988). Initially trophozoites are found in the intestinal lumen and within mucosa (Brandt and Perez-Tamayo 1970). Following attachment to interglandular epithelium, the trophozoites have been found associated with the microulcerations of the mucosa. Symptoms at this stage include non-specific colitis with edematous mucosa and hemorrhage (Pittman and Henniger 1974). Following attachment of amoeba, there is considerable disintegration of epithelial cell layer followed by invasion of submucosa. The human inflammatory response to amoebic invasion is poor. This may be because *E. histolytica* can lyse inflammatory cells (Guerrant *et al* 1981; Salata *et al* 1985). With time the ulcer extends into *lamina propria* and further into *muscularis mucosa*, where progress usually stops prior to perforation. A plug of necrotic debris accumulates at the center of the ulcer. Trophozoites are found in the leading edge at the base of the ulcer (Brandt and Perez-Tamayo 1970; Prathap and Gilman 1970). Ulcers are typically "flask-shaped" (Brandt and Perez-Tamayo 1970). Inflammatory response may be seen at the edges of the ulcers and involves mononuclear and giant cells with few neutrophils (Brandt and Perez-Tamayo 1970; Pittman *et al* 1973). Ulceration of mucosa is the hallmark of invasive disease. Ulcers develop more frequently in caecum and ascending colon. In about 20% of acute colitis cases, perforations occur which results in peritonitis (Brandt and Perez-Tamayo 1970). Chronic ulceration results in the formation of a proliferative tuft of remaining mucosa that appears as a mass (termed amoeboma) in the lumen (Brandt and Perez-Tamayo 1970; Prathap and Gilman 1970). Occasionally, trophozoites reach the liver by portal venules or intestinal perforation and produce abscesses. Liver abscesses, which may be