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# Virulence and virulence factors in *Entamoeba histolytica*, the agent of human amoebiasis

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**Abstract**

Human infections with *Entamoeba histolytica* sporadically become pathogenic, unknown triggers converting the parasite to its invasive phenotype. Parasite virulence results from complex host–parasite interactions implicating multiple amoebic and host factors, eliciting host defence responses and parasite resistance to stress caused by the host reactions and changing environments during tissue invasion.


*Keywords:* Amoebiasis; *Entamoeba*; Parasite–host interactions; Stress response; Virulence

## 1. Introduction

Parasites are organisms that live and multiply taking resources from others, while causing variable degrees of damage to the latter. A number of species have evolved to live inside a host. In general, well-adapted parasites do not threaten host survival, implying a delicate balance between host damage and their own profit that allows progression through the life cycle and maintenance of infectivity and transmission, thus the permanence of the species. Parasites profiting from host nutritional resources without causing obvious damage are commensal organisms. In particular circumstances they are or may become pathogenic, i.e. they cause a disease, by breaking down host defence mechanisms and by inhibiting host functions. Whereas pathogenicity and virulence both designate the parasite's capacity to provoke disease, virulence is more specifically associated with the degree of disease severity (e.g. the fatal case rate), pathogen infectivity and tissue invasiveness. Pathogenic microorganisms express virulence factors, which are molecules implicated in the establishment of the pathology and generally required in the processes of adhesion and colonization, tissue invasion, evasion from and inhibition of host immune responses. The ability of pathogens to adapt to and to survive changing environments and to manipulate host responses can also be considered as virulence traits.

*Entamoeba histolytica* is a pathogenic amoeba causing amoebiasis in humans. Its virulence is generally attributed to the capability to destroy tissues through adherence, host cell killing and extracellular matrix (ECM) proteolysis, linked to the expression of a set of virulence factors and commonly evaluated in a hamster or gerbil animal model. The outcome of an infection also critically depends on host genetic determinants and environmental factors. Experimental model systems to study *E. histolytica* infections are contributing to the discovery of new aspects of the biology of amoeba colonization and dissemination in humans. Here, we review current

*Abbreviations:* ALA, amoebic liver abscess; AP, amoebapore; CP, cysteine protease; CRD, cysteine-rich domain; ECM, extracellular matrix; Gal/GalNAc, galactose- and *N*-acetylgalactosamine-inhibitable; GPI, glycosylphosphatidylinositol; GS, glucose starvation; Hsp, heat shock protein; IFN, interferon; IL, interleukin; KERP, lysine- and glutamic acid-rich protein; LPG, lipophosphoglycan; LPPG, lipophosphopeptidoglycan; NK, natural killer; NO, nitric oxide; PPG, proteophosphoglycan; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumour necrosis factor.

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knowledge on the strategies utilized by *E. histolytica* to subvert immunity and to invade tissues, particularly intestine and liver.

## 2. The life cycle of *E. histolytica*

Asymptomatic infections with *E. histolytica* are common, whereas the symptoms of invasive amoebiasis develop in approximately 10% of the infected individuals, resulting in 50 million cases and 100,000 deaths annually [1]. Recent data on prevalence and morbidity suggest that amoebiasis is probably endemic in many less-developed countries [2,3], making this disease a permanent public health problem that needs attention from health authorities. *Entamoeba* has a relatively simple life cycle (Fig. 1) consisting of two stages, the dormant cyst and the vegetative trophozoite stage. The main mode of transmission of amoebiasis is ingestion of *E. histolytica* cysts from contaminated food or water. Excystation in the intestinal lumen produces trophozoites (Fig. 2) that colonize the large intestine (Fig. 3) by adhering to colonic mucins, feed on bacteria of the intestinal flora and divide [2]. Trophozoite populations may reach high densities and aggregate, a process expected to trigger the shift from exponential growth to encystation and which can also be envisaged as a trigger of virulence. An interesting parallel can be drawn with pathogenic bacteria such as *Staphylococcus aureus*, which at low cell density express proteins promoting attachment and colonization, whereas at high cell density, these traits are repressed and the bacteria initiate secretion of toxins and proteases required for dissemination [4]. However, there are no clues indicating that *E. histolytica* communicates through a quorum-sensing like system which initiates encystation and/or pathogenicity, although it secretes numerous proteins and cell activators [5], some of which may act as (auto-) inducers of virulence.

Unlike many parasite species, *E. histolytica* does not depend on a vector for transmission, since cysts are excreted in stools and perpetuate the life cycle by further faecal–oral spreading. Because of its life cycle, *E. histolytica* is considered a group III pathogen, i.e. a microorganism of potential use as an agent of bioterrorism, as classified by the National Institute of Allergy and Infectious Diseases. In addition, due to its relatively easy transmission and its impact in terms of mortality and morbidity it is a class B agent, i.e. a pathogen for which monitoring and diagnosis should be improved, according to the Center for Disease Control.

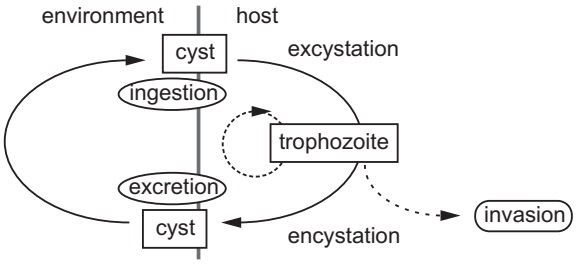


Fig. 1. *Entamoeba histolytica* life cycle and infection of human hosts. The life cycle of *E. histolytica* consists in alternating environment-resistant contaminating cysts and vegetative trophozoites. Infection occurs directly upon cyst ingestion, without intermediate hosts as a vector. Cysts differentiate into trophozoites that colonize the intestinal mucus, multiply and produce new cysts. Invasive infection occurs only in approximately 10% of the carriers.

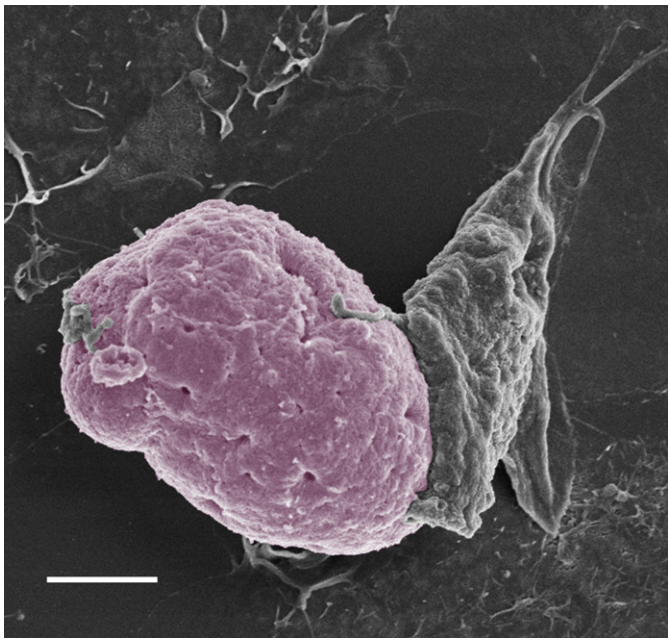

Fig. 2. Interaction of virulent *E. histolytica* with human liver sinusoidal endothelial cells. Scanning electron microscopy micrograph of a trophozoite (highlighted in colour) in contact with human liver sinusoidal endothelial cells [92]. Scale bar 5 μm.

## 3. The invasive infection by *E. histolytica*

For unknown reasons, commensal trophozoites may become invasive, i.e. they start to destroy the muco-epithelial barrier thus inducing the overproduction of mucus, killing host cells and provoking inflammation and subsequently dysentery (Fig. 3). Breaking the intestinal barrier and the blood vessels causes the loss of water and blood in the stools. Therefore, at the macroscopic level, the detection of blood and mucus in diarrhoeal stools is an index to suspect amoebic dysentery, but a more precise diagnosis is mandatory to discriminate from bloody diarrhoea caused by infection with enteropathogenic bacteria. Having reached the vessels present in the mucosa, trophozoites may disseminate via the afferent blood flow of the portal vein system and cause damage to other organs, in particular, amoebic liver abscesses (ALAs) (see review [6]). These are the most common manifestations of extraintestinal amoebiasis.

## 4. Human colon colonization by different *Entamoeba* species

Due to the presence of diverse *Entamoeba* species in the human colon including non-pathogenic *Entamoeba dispar*, *Entamoeba coli* and *Entamoeba moshkovskii*, the causative agent of amoebiasis, *E. histolytica* wore many names for more than 100 years [7]. Based on biochemical and immunological