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Invited Review

Genomic and proteomic approaches highlight phagocytosis of living and apoptotic human cells by the parasite Entamoeba histolytica

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Abstract

Phagocytosis plays a major role during the invasive process of the human intestine by the pathogenic amoeba *E. histolytica*. This parasite is the etiologic agent causing amoebic dysentery, a worldwide disease causing 50 million of clinical cases leading to about 100,000 deaths annually. The invasive process is characterized by a local acute inflammation and the destruction of the intestinal tissue at the invasion site. The recent sequencing of the *E. histolytica* genome has opened the way to large-scale approaches to study parasite virulence such as processes involved in human cell phagocytosis. In particular, two different studies have recently described the phagosome proteome, providing new insights into the process of phagocytosis by this pathogenic protozoan. It has been previously described that *E. histolytica* induces apoptosis and phagocytosis of the human target cells. Induction of apoptosis by the trophozoites is thought to be involved in the close regulation of the inflammatory response occurring during infection. Little is known about the molecular mechanisms responsible for induction of apoptosis or in the recognition of apoptotic cells by *E. histolytica*. In this review, we comment on the recent data we obtained after isolation of the early phagosomes and the identification of its associated proteins. We focus on the surface molecules potentially involved in human cell recognition. In particular, we propose several parasite molecules, potentially involved in the induction of apoptosis and/or the phagocytosis of human apoptotic cells.
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1. Introduction

Human intestine is a major target of pathogenic micro-organisms through oral ingestion of contaminated food or water. Enteric infections resulting in diarrhoeal diseases remain a leading public health problem. It has been estimated that 2–4 billion cases of diarrhoea occur annually in developing countries, causing about 2.2 million deaths. The highest incidence is observed for children below the age of 5 years (Thapar and Sanderson, 2004). Dysentery is a severe manifestation of diarrhoea caused by either pathogenic enterobacteria or by the amoeba parasite *E. histolytica*. In patients developing amoebic dysentery (amoebiasis), a severe intestinal tissue destruction is observed with the presence of apoptotic and necrotic cells (Stanley, 2001). The health impact of amoebiasis, a disease still underestimated by the major public health programs, has been better appreciated with the improved diagnostic methods. For instance, an epidemiologic study performed in Hue City (Vietnam), showed that 21 of 100,000 inhabitants have an amoebic liver abscess (Blessmann et al., 2002). In Dhaka, Bangladesh, a cohort of preschool children followed prospectively exhibit an annual prevalence of 44% amoebic infections (Haque et al., 1998). Globally, amoebiasis accounts for 50 million clinical cases and 100,000 deaths annually.

Amoebiasis is initiated by ingestion of the quadrinucleate cyst of *E. histolytica*, which excysts in the intestinal lumen and produces trophozoites that colonize the large intestine. The first stage of the invasive process is achieved by adhesion of the trophozoites to colonic mucins via a parasite surface galactose and *N*-acetyl-D-galactosamine (Gal/GalNAc) lectin (Petri et al., 2002). In addition, activation of parasite motility is a pre-requisite for the initiation of intestine invasion. Hallmarks of amoebiasis include: degradation of the extracellular matrix (ECM) by amoebic proteases, production of toxic factors, activation of cells from the host immune system, killing and

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phagocytosis of human cells, resulting in the establishment of an acute inflammation. The host cells exhibit an innate immune response, characterized by NF-kB activation and secretion of cytokines, activating the recruitment of neutrophils and macrophages to the invasion site (Seydel et al., 1998a,b). An experimental model using human intestine xenograft in severe combined immunodeficiency (SCID) mice, which reproduces early steps of the intestinal *E. histolytica* invasion, has been used for a molecular analysis of human tissue response against the parasite invasion (Seydel et al., 1997). Data obtained by microarray analysis on the grafted invaded tissue suggest that the human colonic responses to *E. histolytica* resembles those seen during inflammatory bowel disease (Zhang and Stanley, 2004). In particular, they showed an increase in the expression of similar genes encoding cytokines, chemokines and mediators involved in the immune and inflammatory responses. Hence, the tissue inflammatory response during amoebiasis is initiated and fuelled by a combination of human and amoebic factors and ultimately leads to neutrophil-mediated intestinal destruction (Seydel et al., 1998a,b).

Although *E. histolytica* can infect a range of different organs, the most frequently observed form of extra-intestinal amebiasis is liver abscesses. Amoebiasis can thus be considered as an infectious disease caused by an unique microorganism and resulting in two distinct clinical manifestations: the intestinal dysentery and the formation of hepatic abscesses.

In this review, we comment the phagocytic process of *E. histolytica*, a major parasite virulence activity, in light of new data obtained from proteomic analysis of isolated *E. histolytica* phagosomes (Marion et al., in press; Okada et al., 2005) and from the recent completion of the *E. histolytica* genome project (Loftus et al., 2005). In particular, we focus on the identification of potential surface molecules involved in phagocytosis of human apoptotic cells by the parasite during the invasion process.

2. Apoptosis signalling and phagocytosis of apoptotic cells

In metazoans, phagocytes are specialized cells involved in tissue homeostasis and host defence against pathogen infections. In higher eukaryote organisms, phagocytosis can be also integrated in specific complex processes such as embryogenesis or angiogenesis. Specialized phagocytes (e.g. macrophages, dendritic cells and neutrophils) ingest senescent red blood cells, dead cells and pathogens. In lower unicellular organisms such as amoeba, phagocytosis is crucial for the internalization of nutrients from their surrounding medium, suggesting that the phagocytic process in mammalian cells could have evolved from an ancient mechanism. The process of phagocytosis can be dissected in several steps that have been characterized according to morphological and biochemical criteria: (i) phagocytosis is initiated by the binding of particles or cells to surface receptors of the phagocytic cell; (ii) the interaction between ligands and receptors triggers a series of events, including the reorganization of the cytoskeleton that leads to pseudopod extension; (iii) the pseudopods close around the particle to form a phagosome, which fuses sequentially with the early and late endosomes and, finally (iv) the phagosome fuses with lysosomes, leading to the digestion of the internalized particle (Fig. 1).

Recent findings indicate that the specificity of the interactions between surface receptors and the particle triggers a unique signal that will guide the fate of the phagocytozed particle and the response of the phagocytic cell (Stuart and Ezekowitz, 2005). These findings emphasize the central role of the receptor recognition specificity and the diversity of the phagosome functions. The molecular mechanisms involved in Fc and C3 receptor-mediated phagocytosis have been described in the literature and will not be detailed in this review (for reviews: Cox and Greenberg, 2001; Swanson and Hoppe, 2004; Stuart and Ezekowitz, 2005). We will focus on the phagocytosis of apoptotic cells, an attractive phenomenon in regard to the pathogenic process triggered by *E. histolytica* since the fast and efficient uptake of dying cells may participate in the control of inflammation during amoebiasis.

During tissue inflammation, phagocytosis has indeed emerged as an important mechanism for the clearance of apoptotic cells (Maderna and Godson, 2003). Apoptosis is characterized by distinct morphological and biochemical changes that take place upon the activation of the caspase protein family. Caspases are usually expressed as inactive forms, the procaspases, which are processed by proteolysis upon initiation of an apoptotic signal (Nicholson, 1999). Two main apoptotic pathways result for the activation of caspases. The first is induced upon the binding of transmembrane death receptors (e.g., TNF-R1, Fas, Death) with their cognate ligands, resulting in the activation of caspase-8 and -10, with concomitant activation of the caspase-3 and -7. The second apoptosis network, which can be initiated by various forms of stress, requires caspase-2-dependent disruption of the mitochondrial membrane and release of mitochondrial proteins, including cytochrome C. Upon its release, cytochrome C cooperates with Apaf-1 to activate caspase-9 that in turn activates procaspase 3. The phagocytes discriminate normal cells from cells undergoing apoptosis by an early appearance of “eat me” signals on the surface of the dying cell. The best characterized of those events is the expression of unusual amounts of the anionic phospholipid, phosphatidylserine (PS), in the outer leaflet of the plasma membrane of dying cells.

A variety of molecules present on the surface of the phagocytic cells are involved in the adhesion of the apoptotic bodies, in the initiation of the engulfment process, as well as in the regulation of their subsequent destruction. Phagocytosis of apoptotic cells can be described in two separate steps: (i) individual or multiple engagements of several surface adhesion molecules, including CD14, CD68, and $\alpha v\beta 3$ integrin, result in the adhesion of the dying cell to the phagocyte; (ii) cell ingestion through specific receptors occurs when PS is exposed on the apoptotic cell surface.

In humans, receptors involved in phagocytosis of apoptotic cells include members from the scavenger receptor

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