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Significance of Calcium Pathogenesis of *E. histolytica*

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Abstract

In nearly all eukaryotic systems, calcium signaling is a crucial component in a number of essential processes. It is accepted that it might likewise be a significant flagging arrangement of the protist parasite *Entamoeba histolytica*. Ca2+ signaling is thought to be linked to the processes that lead to *E. histolytica's* invasion and pathogenesis, which include motility, adhesion, cytolysis, phagocytosis, and trogocytosis. There is a huge number of Ca2+ restricting proteins (CaBPs) in *E. histolytica*, and some of these proteins appear to be related with various strides in pathogenesis. The fact that this parasite's genome contains 27 EF-hand-containing CaBPs in addition to a number of other proteins with Ca2+ binding domains or motif suggests an intricate calcium signaling network. *E. histolytica* lacks a typical calmodulin like protein, unlike other eukaryotes. None of the CaBPs show grouping closeness with a common calmodulin, broad underlying likeness has been found notwithstanding absence of huge practical crossover with that of average calmodulins. The identification of CaBPs (EhCaBP1, EhCaBP3) that are able to directly bind actin and modulate actin dynamics is one of the distinguishing characteristics of *E. histolytica*. Direct connection of CaBPs with actin has not been found in some other framework.

Amoeba CaBPs (EhC2Pk, EhCaBP1, EhCaBP3, and EhCaBP5) participate in pseudopod formation and phagocytosis, two processes that require actin dynamics. This suggests that a novel Ca2+ signaling pathway has developed in this genus because none of these *E. histolytica* CaBPs has homologs in organs other than different Entamoeba species.

Keywords: Protist parasite; Pathogenesis; Motility; Adhesion; Phagocytosis; Calmodulin

Introduction

Human amebiasis is caused by the protist parasite *Entamoeba histolytica*, which is a major public health issue in developing nations. Even though research into the disease's pathobiological mechanisms has progressed significantly over the past few decades, little is known about the molecular pathways that lead to tissue damage and invasion in both intestinal and extraintestinal diseases. Clear linkage between the genotype of the parasite with intrusive infection or with extraintestinal attack has not been seen, however various destructiveness factors have been recognized lately. In amebiasis, the relationship between the host and the parasite is also influenced by host factors, which include the microflora of the gut and host genes like leptin. In addition to providing food, gut bacteria also provide an anaerobic environment and pH that encourage trophozoites to multiply and transform into cysts. It is progressively trusted that the stomach climate and parasite genotype, along with the host genotype, all connect to establish the right climate for *E. histolytica* to attack. We do not, however, have a clear understanding of the nature of these interactions or how they ultimately affect the parasite's capacity to invade tissues [1].

E. Histolytic a's homeostasis mechanism for Ca2+

One of the numerous and ubiquitous second messengers that mediates pathways by altering the shape, charge, and electrostatic interaction of effector molecules downstream is Ca2+. Cells have developed a "signaling toolkit" that sequesters or compartmentalizes Ca2+ and releases it as needed to mediate response in the presence of a stimulus. Ca2+-mobilizing signals in this toolkit activate a variety of ion channels and transport systems to regulate the level of Ca2+ in various cellular compartments. A collection of CaBPs, Ca2+ buffers, and Ca2+-regulated enzymes subtly transform these Ca2+ signals into a cellular response when Ca2+ is released. Ca2+ is quickly removed from the cytoplasm by a variety of pumps and exchangers following the initiation of a response by activating the appropriate pathway. It is unclear whether the majority of the molecules required for the release and sequestration of Ca2+ in response to a signal are encoded by *E. histolytica*. There are only a few molecules with genes for putative Ca2+ ATPases that have been identified. Three of these molecules belong to PMCA and two to SERCA, both of which are found in vacuoles and the cytoplasmic network, respectively. Two *E. histolytica* (Eh) Ca2+ ATPases, EhSPCA (secretory pathway calcium ATPase) and EhCCX (cation exchanger), have recently been identified. Some cytoplasmic vesicles have these on their membrane [2].

Interestingly, trophozoites' cell death was reduced and virulence was increased when EhCCX was overexpressed. Ionophore releasable Ca2+ is found in *E. histolytica*, making up about 70% of the total Ca2+ pool that can be divided into two parts. One of them is sparked by the second messenger inositol 1,4,5-tri-phosphate (Ins(1,4,5)P3), which causes endoplasmic reticulum-like structures to release internal Ca2+. The second one responds differently to Ins(1,3,4,5)P4 [3].

Although it appears that these two second messengers interact with two distinct Ca2+ stores, the existence of a connection between them in this organism is unknown. Numerous Ca2+-dependent nucleotidases, such as Ca2+ dependent ATPase/ADPase, Ca2+ dependent thiamine phosphodiesterase, and acid phosphatase, are also encoded by *E. histolytica*. The calpain like protein is believed to be related with apoptosis of the parasite in light of the fact that its level is expanded

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during modified cell passing of trophozoites. Some of the nucleotidase enzymes are present in the inner membrane of cytoplasmic vacuoles that may or may not be phagolysosomes, whereas it was also found in the cytoplasm and near the nucleus. Additionally, it is unclear whether these enzymes contribute to this organism's calcium homeostasis. In *E. histolytica*, a repertoire of 27 CaBPs with multiEF-hands was discovered through genomic analysis [4, 5].

Cells for interest

E. histolytica adhesion to target cells is necessary for subsequent cell lysis and tissue invasion, as clearly demonstrated. *E. histolytica*'s hydrolytic and cytotoxic molecules or the stimulation of the apoptotic pathway that begins after contact with the parasitic cells can directly cause the death of the target cells. Numerous proteolytically active genes are encoded and expressed by amebic cells. Among these, cysteine favorable to teinase 5 (Ehcp5) has acquired consideration since it is situated on the cell surface and due to the shortfall of a practically dynamic homolog in the nonpathogenic species *E. dispar*. Porin like proteins of *E. histolytica*, amebapores, were likewise ensnared in cytolysis done by amebic cells. After *E. histolytica* interacts with target cells, one of their outcomes is a significant increase in Ca2+ levels. The death of the target cell was slowed down by blocking Ca2+ channels. Because the purified protein itself raises Ca2+ levels in target cells, it is hypothesized that Gal/GalNAc lectin initiated this. However, upon contact with *E. histolytica*, the mechanism by which target cells release Ca2+ is unclear [6, 7].

Phagocytosis process

Phagocytosis is closely related to *E. histolytica*'s biology. It has a high rate of pinocytosis and phagocytosis, resulting in a renewal of the plasma membrane every 30 minutes. It phagocytoses a variety of cells, including RBCs, bacterial cells, live and apoptotic cells from mammals, and so on. According to a number of reports, phagocytosis is essential to the virulence of amebae. The observed direct positive relationship between an isolate's phagocytic ability and virulence potential constitutes the majority of the evidence. In general, less virulence is correlated with a lower phagocytic potential. In addition, a phagocytosis deficient mutant was found to be virulent. This mutant's level of EhCaBP1 was found to be reduced several fold when it was analyzed, indicating that EhCaBP1 may be involved in phagocytosis. Chelation of Ca2+ in the cytoplasm also inhibited phagocytosis, demonstrating that Ca2+ plays a crucial role in the process. A tentative molecular pathway for phagocytosis in *E. histolytica* has been outlined by a number of studies in recent years. All of these studies demonstrate that Ca2+ plays a crucial role during the initiation phase and phagosome formation [8, 9].

Molecular mechanism

The recruitment of an EhC2PK protein kinase with a C2-domain at the particle attachment site kickstarts phagocytosis. When C2 binds to membranes in the presence of Ca2+, this recruitment occurs. It is dependent on the C2 domain and the Ca2+ domain. The phagocytosis complex, which begins with cups and moves toward phagosomes, is thought to be triggered by the recruitment and enrichment of EhC2PK. Multiple EhCaBPs, including EhCaBP1, EhCaBP3, and EhCaBP5, are required for the phagocytosis complex's formation. At the phagocytic stage, EhC2PK recruits EhCaBP1, and Ca2+ is not required at this stage. In the presence of Ca2+, EhCaBP1 binds to and recruits the atypical protein kinase EhAK1 once it reaches the phagocytic initiation site. Through the subunit EhARPC1, EhAK1 recruits proteins of the actin-related protein (Arp 2/3) complex. Arp2/3 complex proteins then bind CaBP EhCaBP3, which resembles calmodulin. This step requires the presence of Ca2+. Because there is no conserved gene in this system, it is believed that *E. histolytica* does not contain a typical calmodulin. EhCaBP3 is thought to be the closest homolog due to its high degree of sequence similarity to calmodulins (approximately 49%). In the presence of Ca2+, both EhCaBP3 and EhCaBP5 bind atypical myosin 1B. It has been demonstrated that phagocytic machinery relies heavily on myosin 1B. Myosin 1B–EhCaBP3 complex involvement in pseudopod fusion and subsequent membrane separation has been clearly demonstrated by imaging. Although the results do indicate involvement in pseudopod fusion, it is unclear what the role of EhCaBP5 is in relation to its interaction with myosin 1B [10-12].

Trogocytosis

Trogocytosis has as of late been demonstrated to be a clever instrument of target cell killing and virulence of *E. histolytica*. The trophozoites will generally ingest sections of live human objective cells that lead to target cell demise. Amebic trogocytosis has been used to describe this process. The AGC family kinase 1 gene, which is only present during the trogocytic event but not during phagocytosis, is likely to initiate the process. The process is then mediated by EhC2PK in a manner that is comparable to that of phagocytosis. In this way, Ca2+ additionally assumes a significant part in trogocytosis [13, 14].

Conclusion

The surprising part is that Ca2+ and CaBPs play a significant role in a few systems, like phagocytosis, that none of the other eukaryotic systems have. In addition, this organism's direct involvement of CaBPs in regulating actin dynamics is quite novel. This novel pathway for controlling phagocytosis may have developed in response to a situation in which the rate of phagocytosis and endocytosis is extremely high, resulting in the complete recycling of the membrane every 30 minutes. A red blood cell's phagocytosis is complete within 30 seconds of attachment, according to live-cell imaging data analysis. The mobilization of these EhCaBPs may not cause time delays following a particle's binding to the cell surface because Ca2+ signaling is a rapid response. During phagocytosis, rapid imaging of the mobilization of various proteins may help us comprehend the nature of this rapid assembly process. Ca2+'s involvement in numerous other amebic processes has not been examined. Since the genome of *E. histolytica* contains a lot of CaBPs, it should come as no surprise that Ca2+ signaling controls a lot of the pathways that affect *E. histolytica's* overall biology [15].

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Conflict of Interest

None

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