Rapid egress of *Trypanosoma cruzi* follows actin cytoskeleton rearrangement and membrane rupture.

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The protozoan parasite *Trypanosoma cruzi* is the etiological agent of Chagas' disease, a deadly and vector-borne zoonotic disease of poverty that affects 6-7 million people mostly in South and Central America and which lacks vaccines and effective therapeutics. Chagas' disease arises as a direct consequence of the lytic cycle of *Trypanosoma cruzi* in the mammalian host. While invasion is well studied for this pathogen, study of egress has been largely neglected. Here we provide the first description of *T. cruzi* egress documenting a co-ordinated mechanism by which *T. cruzi* engineers its escape from the host cells in which it has proliferated, and which is essential for maintenance of infection and pathogenesis. Our results indicate that this parasite egress is a sudden event involving co-ordinated remodeling of host cell cytoskeleton and subsequent rupture of host cell plasma membrane. We document that host cells maintain plasma membrane integrity until immediately prior to parasite release and report the sequential transformation of the host cell's actin cytoskeleton from normal meshwork in non-infected cells to spheroidal cages - a process initiated shortly after amastigogenesis. Quantification revealed a gradual reduction in F-actin over the course of the lytic cycle and using cytoskeletal preparations and electron microscopy we were able to observe disruption of the F-actin proximal to intracellular trypomastigotes. Furthermore, western blotting experiments revealed actin degradation driven by parasite proteases, suggesting stage-regulated degradation of cytoskeleton as a principal component controlling the initiation of egress. Taken together our results provide the first description of the cellular mechanism which regulates the lytic component of *T. cruzi* lytic cycle. We show graphically how it is possible to preserve the envelope of the host cell plasma membrane during intracellular proliferation of the parasite and how in cells packed with amastigotes differentiation into trypomastigotes may trigger sudden egress.

Keywords: Egress, *Trypanosoma cruzi*, Lytic cycle, Microfilament, Host-parasite relationship, Trypomastigote, Amastigote, Cell invasion, Protozoan, Chagas' disease