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Are determinants of cell entry and virulence synonymous for American trypanosomes?

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Introduction

Not everyone who contracts *Trypanosoma cruzi* goes on to manifest the symptoms of Chagas disease. Although there is little evidence for spontaneous cure of what is normally a life-long infection, there is a profound heterogeneity in the pathologies arising. This stems partly from the parasite genotype and partly from the genotype and immune status of the infected host. A close cousin of *T. cruzi*, *Trypanosoma rangeli* is also infectious, causing life-long infections in humans, but it is completely apathogenic.

Methods

We coated latex beads in parasite virulence factors as trypanosome facsimiles and trans-expressed *T. cruzi* virulence factors in *T. rangeli* as challenges with which to probe their role in adhesion, uptake and eliciting host cell responses from epithelial cell lines expressing key reporter constructs.

Results

Our investigations of *T. cruzi* surface determinants using beads and *T. rangeli* as vehicles have confirmed the critical importance of trans-sialidase (TS) and trans-sialidase like (TSL) proteins in host cell entry. We have shown that while both active and enzymically inactive TS proteins induce actin-dependent, caveolin mediated endocytosis, enhanced uptake requiring G-protein mediated signalling is critically dependent on transsialidase activity. Our complementary use of heterologous expression for surface determinants including TS, TSLs and cruzipain in *T. rangeli* has led to the elucidation of the requirements for *T. cruzi* uptake and targeting to the autophagous and lysosomal compartments of the host cell, which in turn dictate the parasites potential for survival and propogation in epithelial cells.

Discussion

The results reinforce the importance of transsialidase as a key mediator of cell entry and reinforce its role in virulence, emphasizing the prospect of transsialidase activity as potentially important therapeutic target. For *T. rangeli*, the results uncover cryptic life-cycle stages and the prospect of orally delivered vaccine which elicits appropriate immune responses for protection against Chagas disease.

Keywords: Transsialidase, Autophagy, Intracellular, Virulence