Trypanosoma cruzi: molecular mechanisms of host-parasite relationships

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Chagas' disease is a chronic, debilitating and incapacitating illness, caused by the protozoan parasite Trypanosoma cruzi when infective trypomastigotes invade host-cells. Our group has previously shown that one member of the Tc85 family (Tc85-11) is involved in the adhesion step of T. cruzi invasion of mammalian host cells. Tc85 belongs to the gp85/transialidase superfamily, with approximately 740 genes and almost the same number of pseudogenes present in the genome of the parasite. Three major questions were asked to understand the mechanism of trypomastigote invasion: a. Are other family members also adhesion proteins? b. Which sequences are involved? c. Which signaling pathways are triggered?

In order to answer the first question, thirty new genes encoding members of the Tc-85 family were isolated and characterized from a Tc-85-enriched cDNA library. Similarly to the results described in the genome project, approximately 50% were pseudogenes. Multiple variants of previously described Tc-85 motifs such as “Asp box”, “RGD”, “peptide G” and other conserved sequences were identified within this group, showing the high sequence variability among the family members. Two isolated Tc-85 protein variants (Tc85-45p, Tc85-12p) were selected for characterization of their binding properties. Both Tc85-45 and Tc85-12 showed a specific binding to laminin and fibronectin in addition to LLC-MK2-derived extracellular matrix and entire LLC-MK2 cells with Tc85-45p showing the strongest binding in all cases. Lactose did not inhibit binding, suggesting that host-cell surface carbohydrates are not involved in the interaction. Adhesion of Tc85-45p to the host cells, but not Tc85-12p, is inhibited by RGD, a well known ligand to integrins. These data led us to speculate that the Tc-85 gene family encodes a variety of structurally similar glycoproteins which, however, differ in motifs sufficiently to allow binding to different mammalian host molecules. These multiple functions in the glycoprotein family enable the parasite to overcome the barriers of cell membranes, extracellular matrices and basal laminae.

The conserved FLY domain (VTXVNFLYNR), present in all members of the gp85/trans-sialidase glycoprotein family coating the surface of trypomastigotes, significantly increases parasite entry into mammalian cells. FLY, present on the surface of trypomastigotes or on latex beads promotes dephosphorylation and reorganization of CK18 and activation of the ERK1/2 signaling cascade culminating in an increase of approximately 9 fold in the number of parasites/cell. Inhibition of ERK1/2 phosphorylation completely blocks the adhesion of FLY to cells and blocks by 57% the host cell infection by T. cruzi.

Although the interaction mechanism of trypomastigotes with mammalian cells has been intensively studied, a final and integrated picture of adhesive motifs and signal transduction mechanisms involved still remain to be elucidated.

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