Revisiting trypanosome transferrin receptor: unveiling novel insights in localization and ligand uptake

Trypanosoma brucei acquires Fe^{3+} from mammalian hosts through receptor mediated endocytosis of transferrin (Tf). The trypanosome transferrin receptor (TfR) is a heterodimer of ESAG6 and ESAG7 and is attached to the external face of the plasma membrane by a single glycophosphatidylinositol (GPI) anchor at the C-terminus of ESAG6. The TfR is clearly accessible to Tf so how does the trypanosome protect itself against host TfR antibodies? One model has been seclusion of the TfR in the flagellar pocket, effective at protecting it from the cellular arm of the immune system. Based on previous reports on the localisation of TfR all agree on the presence of it in endosomal compartments with some placing it in the flagellar pocket (lumen) and others on the cell surface in presence of canine transferrin which did not bind the expressed TfR.

To characterise the cellular evasion strategies evolved by *T. brucei* to avoid the host adaptive immune system, we have re-visited the expression, localisation and functioning of the TfR. We show that the expression level of TfR varies several folds in cells expressing ESAG6 and ESAG7 from one bloodstream form expression site (BES) to another. We find that the determination of the localisation is affected by the expression level but this is likely due to detection limits and fixation protocol rather than representing a real difference. Next, we took advantage of the endogenous BES7 TfR with GPI-anchors on both ESAG6 and ESAG7 to compare the properties of single and double anchored TfR. We found that the double anchored TfR was expressed at slightly higher (1.4-fold) levels but otherwise had similar properties. Assays of Tf uptake showed that Tf was internalised within a couple of minutes for both single and double anchored receptors.

Together these observations have allowed us to develop a model in which the TfR is distributed all over the cell surface in a similar manner to other receptors. We have previously shown that Tf binding along with the presence of N-linked glycans effectively mask exposed parts of the receptor. Here we add cellular mechanisms of the likely rapid endocytosis of any TfR- antibody complex along with a low copy number effectively reducing the residence time of TfR immunoglobulins on the cell surface.

We would like to thank Professor Piet Borst for the gift of TfR antiserum.