

Abstract

The development of *Trypanosoma brucei* in its mammalian host is marked by a distinct morphological change as replicative “slender” forms differentiate into cell-cycle arrested “stumpy” forms in a quorum-sensing dependent manner. Although stumpy forms dominate chronic infections at the population level, the proportion of replicative parasites at the individual cell level and the irreversibility of arrest in the bloodstream is unclear. Here, we use an ex vivo assay and a developmentally-deficient mutant to demonstrate that developmental cell cycle arrest is definitively irreversible in both acute and chronic infection stages in mice. Further, an analysis of replicative capacity and the transcriptome profile at the single cell level demonstrates a temporal hierarchy exists whereby cell cycle arrest and transcriptomic adaption to stumpy development precedes irreversible commitment and morphological change. Unexpectedly, we show that once trypanosome infections are established, proliferative parasites are exceptionally scarce. This challenges the ability of trypanosomes in the circulatory bloodstream to sustain the infection by proliferation or antigenic variation, these parasites instead being overwhelmingly adapted for transmission.