Experimental digestive Chagas disease: spatio-temporal infection dynamics, immuno-pathological mechanisms and the prospect of functional cure with trypanocidal benznidazole chemotherapy

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Digestive Chagas disease (DCD) is an enteric neuropathy caused by infection with the protozoan pathogen *Trypanosoma cruzi* that affects ~1 million people. Parasitism of the GI tract provokes a type 1 inflammatory response, which causes collateral damage to the enteric nervous system (ENS) and dysfunctional peristalsis, progressing to digestive megasyndromes in severe cases. Beyond this, little is known about the kinetics, underlying molecular/cellular mechanisms or determinants of susceptibility. The lack of a robust, predictive animal model has held back research in these areas. We screened a series of mouse models using gastrointestinal tracer assays and *in vivo* infection imaging systems to discover a subset exhibiting chronic digestive transit dysfunction and significant retention of faeces in both sated and fasted conditions. The colon was a specific GI region of tissue parasite persistence, delayed transit and dramatic loss of myenteric neurons, as revealed by whole-mount immunofluorescence analysis. Immune transcriptome profiling of colon tissue from DCD resistant BALB/c and susceptible C3H mice identified the macrophage scavenger receptor MARCO as significantly associated with disease severity. Next, we tested the hypothesis that benznidazole-mediated cure of infection translates into alleviation of DCD pathology. Sterilisation of infection by early treatment (6 weeks post-infection) resulted in sustained and complete reversal of GI transit delay, accompanied by an ENS tissue repair transcriptional profile dominated by glial cell markers. However, late treatment (24 weeks post-infection) only led to partial reversal of the DCD phenotype, suggesting the accumulation of permanent tissue damage during chronic infections. Importantly, benznidazole treatment failed to cure 40% of mice and parasite relapse coincided with a worsening of disease, but not to the level seen in untreated controls. These data prove that DCD pathogenesis is sustained by enduring *T. cruzi* infection and can be interrupted by sterilising anti-parasitic chemotherapy. However, they also show that if treatment is delayed there is a risk that parasite-induced enteric neuromuscular tissue damage and dysfunction will become irreversible.