What are the drivers of enteric neuropathy in experimental Chagas disease?

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Chagas disease, caused by the protozoan parasite *T. cruzi*, affects ~7 million people worldwide. Around 30-40% of those infected develop chronic cardiac or gastrointestinal (GI) sequelae. GI disease is associated with a high morbidity, but the mechanisms responsible for the underlying enteric agangliosis and megasyndromes are largely unknown. The leading hypothesis for enteric nervous system pathology has been collateral damage induced by reactive nitrogen species, synthesised by iNOS-expressing myeloid cells during the acute phase immune response. This hypothesis has been questioned since bioluminescence imaging led to the discovery of chronic parasite reservoirs in the colon, which suggests an ongoing role for the infection in sustaining pathogenesis. Recent work has shown that C3H/HeN mice infected with TcI-JR parasites develop GI dysperistalsis, which is a common symptom of human digestive Chagas disease. This project aims to provide insight into the mechanisms responsible for enteric neuropathy in this mouse model. We conducted a histopathological analysis of colon tissue and found a significant increase in cellular infiltration in the smooth muscle of chronic Digestive Chagas Disease (DCD) mice, but not when a less pathogenic *T. cruzi* strain (TcVI-CLBR) was used. This inflammation was hyperfocal to the GI smooth muscle, adjacent to the adipose rich mesentery in the proximal colon. There was also evidence of focal fibrosis, high iNOS expression and neuronal damage. In ongoing *in vivo* experiments, we are investigating the effects of anti-parasitic and immunomodulatory treatments on the initiation of gut dysfunction in the DCD model, which occurs between 2 and 3 weeks post-infection. Benznidazole treatment suppressed the parasite burden below the limit of detection and prevented the initiation of gut dysfunction.

Elimination of CD8+ T cells (which are critical for parasite control) by anti-CD8 immunotherapy increased the parasite burden by 19 fold and had no impact on the gut dysfunction phenotype. Interestingly, treatment with the broad immune suppressant cyclophosphamide completely reversed the GI peristalsis defect, even though the parasite load increased by 15 fold.

The results suggest an antagonistic interaction between parasites and immune action is key to the initiation of gut dysperistalsis, but one where CD8+ T cells are not critical pathological effectors. These results are generating insights into the early host-parasite interactions that drive digestive Chagas disease pathogenesis.