Transcriptomics of the immune response in Chagas heart disease

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Chagas disease, caused by infection with *Trypanosoma cruzi* parasites, is the most frequent cause of infectious cardiomyopathy in the world. Chagas heart disease (CHD), an inflammatory cardiomyopathy, develops in approximately one-third of chronically-infected people. Why some infected individuals develop cardiomyopathy while others remain asymptomatic for life remain poorly understood.

Here, we used experimental mouse *T. cruzi* infections with differing degrees of cardiac pathology to model different pathological outcomes observed in the clinic. We then used single-cell RNA sequencing (scRNA-seq), spatial transcriptomics and flow cytometry to identify immune signatures associated with differing degrees of CHD. scRNA-seq showed that TcVI-CLBR-infected-BALB/c (mild CHD) and TcI-JR-infected C3H/HeN (severe CHD) mice develop strikingly different immune responses to the parasite in the spleen, with B cells dominating these differences. Severe CHD lead to accumulation of an unswitched, recently-activated B-cell subset with very high expression of *Nr4a1* (Nur77), previously identified as a marker of autoreactive B cells. To specifically track B cells reacting to the parasite vs those reacting to host cardiac tissues, we developed B-cell tetramers to detect, by flow cytometry and side-by-side, *T. cruzi*-specific and cardiac-specific B cells. Both parasite-specific and cardiac-specific B cell responses were robustly activated in the spleen of TcI-JR-infected C3H/HeN (severe CHD) mice. However, showing important differences in their functional profile, spleen-resident cardiac-specific B cells failed to develop germinal centre, class-switching and memory responses to the infection. Further, spatial transcriptomics of heart tissue sections showed a striking accumulation of plasma (B) cells dominating the immune infiltrate in the heart of TcI-JR-infected C3H/HeN (severe CHD) mice.

Thus, our data shows a dominant B-cell immune signature associated with severe CHD, characterised by accumulation of short-lived autoreactive cardiac-specific B cells in the spleen and striking accumulation of plasma (B) cells in the heart of infected mice.