ImmunoTools *special* Award 2014

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IL-17RA-signaling cytokines in the regulation of CD8 T cell immunity to *T. cruzi*

Chagas´ disease, caused by the parasite *Trypanosoma cruzi*, affects 8 million people and imposes a major economic burden due to early mortality and physical disabilities. It is endemic in Latin America but cases are increasing in non-endemic countries, becoming a global concern. Disease progression, from symptomless to severe, are linked to parasite heterogeneity and variable host immune response. Indeed, development of robust $CD8^+$ T cell immunity is a key element of host resistance and T. cruzi persistence and chronic Chagas disease has been associated to suboptimal $CD8^+$ T cell responses. Consequently, defining the nature of $CD8^+$ T cells mediating immunoprotection and the rules governing the maintenance of these cells is crucial for our understanding of the pathogenesis of Chagas disease and also for the design of novel therapeutic and vaccination approaches. Cytokines are central environmental cues that dictate the magnitude and quality of protective $CD8^+$ T cell responses and, thus, emerge as attractive targets for immunointervention. However, our incomplete knowledge about the cytokines, signaling pathways and transcriptional programs involved in the generation of optimal $CD8^+$ T cell immunity holds back possible applications of relevance to human health.

Our long-term goal is to identify new cytokines and pathways involved in the generation and maintenance of protective immunity to the protozoan parasite *T. cruzi.* We reported that IL-17RA and IL-17-producing B cells play critical roles for host protection during experimental *T. cruzi* infection by regulating innate and adaptive immune responses. Furthermore, our preliminary findings show that *T. cruzi*-infected IL-17RA-deficient mice present reduced immunity of specific $CD8^+$ T cells that correlates with increased parasite burden and reduced host resistance. These compelling data support our working hypothesis that IL-17RA-signaling cytokines are critically involved in the regulation of the developmental pathways that determine the

generation of robust protective $CD8^+$ T cell responses to *T. cruzi*. We propose two specific aims:

1- To dissect the mechanisms underlying IL-17RA-mediated regulation of specific $CD8^+$ T cell development. We will delineate the cellular and molecular programs dictated by IL-17RA signaling pathways to determine whether IL-17RA modulates the magnitude and quality of protective $CD8^+$ T cell immunity to *T. cruzi* by affecting expansion, contraction or differentiation. For this, we will perform a detailed comparison of the frequency, phenotype, effector function and transcriptional profile of $CD8^+$ T cells from infected WT and IL-17RA mice, contrasting these profiles with those reported for effector, memory and exhausted T cells. The fluorochrome labeled antibodies from ImmunoTools will be essential for these studies.

2- To establish whether IL-17RA-signaling plays $CD8^+$ T cell intrinsic and/or extrinsic roles in supporting $CD8^+$ T cell immunity. We propose adoptive transfer approaches to test if IL-17RA-signaling cytokines potentiate $CD8^+$ T cell immunity to *T. cruzi* by directly regulating $CD8^+$ T cells (intrinsic mechanisms) and/or by modulating other cell subsets that indirectly regulate $CD8^+$ T cell development (extrinsic mechanisms). According to the results, we will study direct effects of IL-17RA signaling in $CD8^+$ T cells or indirect effects on cell subsets such as $CD4^+$ T cells, dendritic cells and regulatory T cells. One of the approaches will be to culture mouse and human $CD8^+$ T cells with cytokines of the IL-17 family and to determine survival, proliferation and phenotype. For this, the recombinant cytokines and fluorochrome labeled antibodies from ImmunoTools will be critical.

Our studies will provide meaningful data about the role of IL-17RA-signaling cytokines in the regulation of $CD8^+$ T cell immunity to T. cruzi, providing potential new targets for the rational design of therapies for Chagas´ disease and, likely, other chronic infections. We also expect to identify the cellular and molecular programs triggered by IL-17RA-signaling and how they dictate particular $CD8^+$ T cell fates. This knowledge will profoundly impact on fundamental immunology and may provide a rationale for understanding unsuspected effects of IL-17-targeted therapies during human diseases.