ImmunoTools *special* Award 2015

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Trypanosoma cruzi infection: Studying mechanism of T cell hyporesponsiveness and macrophage polarization

Chagas disease is a potentially life-threatening illness caused by the protozoan parasite, *Trypanosoma cruzi*. It is found mainly in endemic areas of Latin American countries. About 7 million to 8 million people are estimated to be infected worldwide, mostly in Latin America. However, in the past decades it has been increasingly detected in the United States of America, Canada, many European and some Western Pacific countries. This is due mainly to population mobility between Latin America and the rest of the world. In the mammalian host, the parasite's biological cycle includes the nondividing, blood-circulating trypomastigotes, which infect the nucleated cells and also the replicating intracellular amastigotes that reside in the cytoplasm of the infected cell as macrophages, dendritic cells and muscle cells. CD4 T cells are important regulators of efficacious anti-parasite immunity. As noted, inflammatory cytokines like TNF and IFN-γ function to activate phagocytic cells to enhance killing of protozoan parasites, and parasite-specific Type 1 helper (T_H1) CD4 T cells are an important source of these cytokines.

Chagas' disease is associated with many immunological alteration, among them an important immunosupresion during the acute phase of the infection. The immune system failure during *Trypanosoma cruzi* infection contributes to the dissemination and installation of the parasite. Several studies have been focused on identifying the mechanisms involved in the immunosupresion observed during this infection; however the molecular mechanisms implicated it is not clear. In addition, during the last years new molecules involved in the negative T cell regulation such as Programmed death receptor 1 and its ligands (PD-1/PD-1L) and E3 ubiquitin ligases (E3-Ub-Lig) have been reported.

In our lab, one of our projects is focused on studying the role of E3-Ub-Lig on the T cell immunosupresion and hiporesponse mechanisms observed during *T. cruzi* infection. It has been demonstrated, that these enzymes control the amount and localization of intracellular signal mediators, limiting T cell activation, proliferation and cytokine production. Moreover, these mechanisms have been shown to mediate the immunosupresion observed during other infections leading to the persistence of the pathogen in the host.

On the other hand, in our lab we are interest to study macrophages since the parasite is able to replicate inside this cells. Therefore, macrophages play a key role in the control of intracellular *T. cruzi* replication. Macrophages are able to polarize to proinflammatory M1 or alternative M2 stages with distinct phenotypes and physiological functions. Previosly, we have demonstrated that an antigen of *Trypanosoma cruzi,* is able to activate alternatively macrophages *in vitro*. This profile of activation allows the uncontrolled growth of the parasite within the macrophages. In addition, we have demonstrated that the growth of the parasite in these macrophages depends critically on the level on arginase. Although the exact role of arginase clearly is not established, this enzyme plays a very important role in a variety of human and experimental diseases. On the other hand, we have shown that alternative macrophages induced during *Trypanosoma cruzi* infection express PD-L2 molecule then can modulate T cell function.

However, how metabolic status regulates macrophage polarization remains not well understood. The mammalian target of rapamycin (mTOR) is a key nutrient/energy sensor that couples nutrient availability to regulation of downstream metabolic processes such as protein synthesis, glycolysis and de novo lipogenesis. It has been recently shown that mTOR pathway regulates macrophage polarization. Therefore we are currently investigating the role of mTOR pathway in macrophage polarization and *T. cruzi* replication.