ImmunoTools *special* Award 2014

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Trypanosoma cruzi infection:

Role and modulation of innate immune pathways that balance the control of parasite replication and the immunopathology.

Chagas disease, caused by the obligate intracellular protozoan parasite *Trypanosoma cruzi*, is a tropical parasitic disease that is currently on the increase interest in non-endemic geographical areas such as the United States and Europe, mainly due to the population movement of infected people. The chronic heart disease is a slowly evolving inflammatory cardiomyopathy that may lead to severe cardiac dilatation, congestive heart failure and death.

In the mammalian host, the parasite's biological cycle includes the nondividing, blood-circulating Tps, which infect the nucleated cells and also the replicating intracellular amastigotes (Am) that reside in the cytoplasm of the infected cell as macrophages (Mo), dendritic cells (DC) and muscle cells. In this disease, the unresolved infection and the inappropriately balanced inflammation could be two important factors that contribute to chronic diseases and to initiate an autoimmune response. For that, the study of activation and modulation of innate immune pathways involved in both the control of *T. cruzi* replication (promotion of inflammation) and the induction of tolerance (restraint of inflammation) is a topic of special interest to find novel therapeutic treatments able to control both the parasite replication and the inflammatory response.

We have several research projects carried on by different PhD students:

- The study of the tryptophan degradation pathway catalysed by the an intracellular enzyme indoleamine 2,3 dioxigenase (IDO) led us to demonstrate that IDO activity is crucial to control T. cruzi replication. We demonstrated that *T. cruzi* Am and Tps are sensitive to the tryptophan downstream metabolite 3-HK, and the therapeutic administration of 3-HK during the acute phase of the infection decreased the parasitemia and improved the survival of lethally infected mice. Also, 3-HK treatment markedly reduced the incidence and the severity of the clinical symptoms by the modulation of the immune response impairing the Th1- and Th2-type specific response, inducing TGF-b-secreting cells and promoting the emergence of regulatory T cells, suggesting that the pharmacologic intervention of IDO pathway could be used as a novel antitrypanosomatid therapeutic strategy. Actually we are assaying treatments using 3-HK combined with known drugs for the purpose of achieving a parasitological cure. The mice are infected and treated with 3-HK combined with different drugs and the survival, parasite load and the induced specific immune response (Th1, Th2, Th17, Treg and memory cells) studied.

- On the other hand, recently it was demonstrated that the aryl hydrocarbon receptor (Ahr), a ligand-activated transcription factor that mediates dioxin toxicity, is required to induce IDO in DC. Moreover, 3-HK can activate this receptor present on naïve T cells with this activation leading to Ahr-dependent Treg generation. It is also plausible that the early TGF-b production observed during T. cruzi infection could lead to Ahr upregulation in DC and T cells, which might potentiate the effect of 3-HK (and other Trp catabolites or endogenous AhR ligands produced during *T. cruzi* infection) on Treg and IDO induction. Experiments to investigate whether *T. cruzi* infection is able to modulate the Ahr expression on DC and T cells, and the role of Ahr expression on *T. cruzi* induced IDO up-regulation and Treg generation are underway.

- Another project in our group is to study the role of Wnt-Frizzed/b-catenin signaling in *T. cruzi* infection. Wnt proteins are secreted, palmitoylated glycoproteins with multiple functions in cell proliferation and migration as well as tissue organization. In the last years, Wnt-Frizzed signaling was also shown to be involved in the modulation of the inflammatory response of macrophages to microbial stimulus. In addition, Wnt–b-catenin signaling in intestinal dendritic cells regulates the balance between inflammatory versus regulatory responses in the gut.

The role of AhR and Wnt signaling during *T. cruzi* infection will be studied in bone marrow derived Mo and DC infected *in vitro* (modulation of ligands, receptors and transcription factors expression) in the presence or the absent of pathway's agonist or antagonist (parasite replication, expression of activation or inactivation surface markers and secretion of cytokines). Also, *in vivo* experimental infections in wt and genetically modified mice will be used to determine the effect of activation or inhibition of each signaling pathway on mice survival, parasite load, damage in target organs, and development of specific immune response (Th phenotype, Treg and memory).