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Role of PPAR ligands in the elicitation of Tregs in an experimental model of Chagas' disease cardiomyopathy

Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi* is mainly transmitted by its biological vectors in endemic areas of Latin America and the Caribbean region. Other forms of transmision, relevant to public health, include blood transfusion and mother-to-child during pregnancy.

Although the disease is generally asymptomatic during the acute phase, around 30% of infected people will develop severe manifestations several years after infection. These include digestive megavisceras (enlargement of the oesophagus and large bowel) and chronic chagasic cardiomyopathy (CCC), a form of dilated cardiomyopathy most widespread in the endemic area. The main cause of the disease seems to be the persistence of parasites, that drive an inflammatory response, that leads to tissue scarring, cardiac dysfunction and, ultimately, sudden death.

Pharmacological treatment of the disease is limited to the acute stage and only two parasiticidal drugs, benznidazole and nifurtimox, have been developed so far. However, they promote severe side effects in a significant number of patients, leading to treatment discontinuation in some cases. Moreover, resistance to treatment has been also shown.

T regulatory cells (Treg) have emerged as key elements for the regulation of autoimmunity as well as in adaptive anti-microbial immune responses. These cells, that can be phenotypically characterized as $CD4^+$ $CD25^+$ $Foxp3^+$ by flow cytometry, promote reduction of inflammation mainly through the secretion IL-10 and TGF-β. Our group has shown in a murine model of Chagas' disease, that T cells bearing a specific TCR clonotype are preferentially recruited to heart. Moreover, these cells

produce significant amounts of IL-10 (1). More recently, using a murine model of acute Chagas' disease, we have shown that treatment of *T.* cruzi-infected mice with 15-deoxy-$\Delta^{12,14}$ prostaglandin J_2, the natural ligand of PPARγ leads to a reduction of the expression of inflammatory mediators in the heart, without significantly affecting mouse survival (2). Recently, it has been shown that patients that remain asymptomatic during the chronic phase have higher frequencies of T regulatory cells (Treg) in peripheral blood than patients that develop CCC (3). Therefore, it may be proposed that CCC is the result of an alteration of the regulatory network, leading to an inflammatory state that, while not controlling parasite multiplication in tissues, promotes tissue injury cardiac dysfunction.

Peroxisome proliferator-activated receptors are members of the nuclear hormone receptor superfamily, involved in lipid and carbohydrate metabolism. It has been shown that these receptors also play a key role in the regulation of inflammation, through the inhibition of transcription of pro-inflammatroy genes like IL-1, IL-6 and TNF-α. Significantly, the PPARα agonist fenofibrate enhances the differentiation of mouse regulatory T cells *in vitro* (4). Moreover, PPARα/γ agonists have been shown to induce the differentiation of functionally active human Treg (5).

In view of the aforementioned evidence, we propose to study the role of PPAR agonists in the development of Treg in a murine model of Chagas disease. Also, we will test whether concomitant treatment with lower doses anti-parasitic drugs with such agonists contribute to limit the parasite burden and reduce inflammation, and whether this reduction is associated with the recruitment of Treg to the heart.

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