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Federico Nicolás Penas, Ph.D
Post Doctoral Fellow

Instituto de Investigaciones en Microbiología y
Parasitología Médica (IMPaM, UBA - CONICET)
Paraguay 2155. Piso 12. Buenos Aires. Argentina

Treatment *in vitro* with PPARγ ligands drives M1-to-M2 polarization of macrophages from *Trypanosoma cruzi*-infected mice

Trypanosoma cruzi (*T. cruzi*), an obligate intracellular protozoan parasite, is the etiological agent of human American trypanosomiasis, a debilitating disease widely distributed throughout Central and South America. Upon infection, the parasite has the ability to invade and multiply within diverse cell types, including macrophages. The acute phase of infection is characterized by the presence of parasites in the host bloodstream and diverse tissues. However, the heart is one of the main targets of this disease, causing serious cardiac alterations in the acute and chronic phases. A crucial step in cardiomyopathy is the infiltration of monocytes and their differentiation into macrophages [1].

Macrophages are a heterogeneous cell population that adapts and responds to a large variety of microenvironmental signals. They play essential roles in immunity and lipid homeostasis and, as professional scavengers, they phagocytize microbes and apoptotic and necrotic cells. Although macrophages play important roles in injury responses and tissue remodeling, it is generally considered that sustained activation of these responses may precipitate pathological states. Moreover, the activation state and functions of macrophages are profoundly affected by different cytokines and microbial products [2,3]. In addition to pathogen clearance, they also regulate the resolution of inflammatory responses. These opposing or polarized activities are initiated and maintained by immunomodulatory factors such as cytokines and microbial products and manifest in distinct activation states. While Th1 cytokines, such as interferon γ (IFNγ), interleukin (IL)-1β, and lipopolysaccharide (LPS), induce a ‘‘classical’’ activation profile (M1), Th2 cytokines, such as IL-4 and IL-13, induce an ‘‘alternative’’ activation program (M2) in macrophages. Moreover, macrophages are considered plastic cells because they can switch from an activated M1 state back to M2, and vice versa, upon specific signals [4,5]. Thus, infectious or inflammatory diseases, such as chronic Chagas cardiomyopathy, may be caused not only by a sustained proinflammatory reaction but also by failure of anti-inflammatory control mechanisms.

Peroxisome proliferator-activated receptor (PPAR)γ is a member of the nuclear hormone receptor family that has been implicated in mediating many metabolic, endocrine and cardiovascular disorders as well as inflammation [6]. Its natural ligand, 15-Deoxy-$\Delta^{12,14}$ prostaglandin J2 (15dPGJ2), has high affinity for PPARγ. Several reports have shown that 15dPGJ2 can repress some genes in activated macrophages and cardiomyocytes, including the

genes for inducible nitric oxide synthase (NOS2), cyclooxygenase 2 (COX2), tumor necrosis factor (TNFα), interleukin 1 beta (IL-1β) and IL-6, and that this repression is partially dependent on PPARγ expression [7,8]. 15dPGJ2 is normally present *in vivo* during the resolution phase of inflammation, suggesting that it may function as a feedback regulator of the inflammatory response [9].

In view of the aforementioned evidence, we propose of the study the effects of PPARγ ligands on the modulation of the inflammatory response and on the phenotypic changes of peritoneal macrophages from *T. cruzi*- infected mice. Since PPARs signaling is involved in switching macrophage polarity to a tissue-repairing phenotype that might ameliorate inflammatory responses, we consider that treatment with PPAR ligands as coadjuvants of the current anti-parasitic treatments might be a new potential therapeutic approach, and may thus open new avenues to the pharmacological resolution of inflammation in Chagas' disease.

References

[1] H.B. Tanowitz, L.V. Kirchhoff, D. Simon, S.A. Morris, L.M. Weiss, M. Wittner, Chagas' disease, Clin. Microbiol. Rev. 5 (1992) 400–419.
[2] J.A. Van Ginderachter, K. Movahedi, G. Hassanzadeh Ghassabeh, S. Meerschaut, A. Beschin, G. Raes, P. De Baetselier, Classical and alternative activation of mononuclear phagocytes: picking the best of both worlds for tumor promotion. Immunobiology 211 (2006) 487–501.
[3] S. Gordon, Alternative activation of macrophages, Nat. Rev. Immunol. 3 (2003) 23–35.
[4] F. Porcheray, S. Viaud, A.C. Rimaniol, C. Leone, B. Samah, N. Dereuddre-Bosquet, D. Dormont, G. Gras, Macrophage activation switching: an asset for the resolution of inflammation. Clin. Exp. Immunol. 142 (2005) 481–489.
[5] A. Mantovani, S.K. Biswas, M.R. Galdiero, A. Sica, M. Locati, Macrophage plasticity and polarization in tissue repair and remodelling, J. Pathol. 229 (2013) 176–185.
[6] J.M. Olefsky, C.K. Glass, Macrophages, inflammation, and insulin resistance, Annu Rev. Physiol. 72 (2010) 219–246.
[7] D.S. Straus, G. Pascual, M. Li, J.S. Welch, M. Ricote, C.H. Hsiang, L.L. Sengchanthalangsy, G. Ghosh, C.K. Glass,. 15-Deoxy-Delta 12, 14-prostaglandin J2 inhibits multiple steps in the NF-kappa B signaling pathway, Proc. Natl. Acad. Sci. USA. 97 (2000) 4844–4849.
[8] E. Hovsepian, F. Penas, N. Goren, 15-Deoxy-delta12,14 PGJ2 but not rosiglitazone regulates MMP-9, NOS-2 and COX-2 expression and function by PPARgamma-dependent and independent mechanisms in cardiac cells, Shock 34 (2010) 60–67.
[9] O.S. Gardner, B.J. Dewar, L.M. Graves, Activation of mitogen-activated protein kinases by peroxisome proliferator-activated receptor ligands: an example of nongenomic signaling, Mol. Pharmacol. 68 (2005) 933–941.