Cellular Immunology and Serum Biology

OMMEGA Publishers
Answering Intelligence
www.ommegaonline.org

Opinion Article Open Access

The Interleukin-17 (IL-17) Puzzle in Chagas' Disease

Jose Mengel[1,2*] and Fabíola Cardillo[3]

[1]Laboratory of Clinical Immunology, Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Av. Brasil Manguinhos, Rio de Janeiro - RJ, CEP, Brazil
[2]Faculty of Medicine of Petrópolis, FMP-FASE, Av. Barão do Rio Branco, 1003 - Centro, Petrópolis - RJ, CEP 25680-120, Brazil
[3]Gonçalo Moniz Institute, Oswaldo Cruz Foundation, R. Waldemar Falcão, 121 - Candeal, Salvador - BA, Brazil

***Corresponding author:** Jose Mengel, M.D.; Ph.D. Laboratory of Clinical Immunology, Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Av. Brasil Manguinhos, Rio de Janeiro - RJ, CEP, Brazil; Email: Jomengel@fiocruz.br

Abstract

In this article, we discuss an alternative explanation for the fact that the production and plasma levels of IL-17 are diminished in patients chronically infected with *Trypanosoma cruzi*, suffering from congestive heart failure. This alternate hypothesis considers the inhibitory pharmacological action of digoxin, a drug commonly used to treat heart failure. We believe this is a significant point to be further studied as IL-17 was initially considered to be heart-protective. Therefore, our argument has profound therapeutic implications.

Received Date: October 20, 2017
Accepted Date: November 11, 2017
Published Date: November 16, 2017

Citation: Mengel, J., et al. The Interleukin-17 (IL-17) Puzzle in Chagas'Disease (2017) J Cell Immunol Serum Biol 3(2): 120- 121.

DOI: 10.15436/2471-5891.17.1714

Introduction

Trypanosoma cruzi is the causative agent of Chagas' disease, a neglected condition[1]. The parasite is transmitted to humans by infected bugs[2]. The disease has two distinct phases[3]. The acute phase is characterized by the presence of the parasite in the bloodstream[4]. During the acute phase, an effective immune response is settled to control parasite replication in the tissues[5]. NK, T, and B cells are crucial to mediate parasite clearance through the production of interferon-γ, interleukin-17 and specific antibodies[4-7]. Immunity cannot sterilize the host, thus leading to infection persistence and therefore, a chronic disease[5]. The chronic illness affects mainly the heart, esophagus and large intestine[2]. Its pathogenesis is still unclear, but a chronic inflammatory reaction in the affected organs may justify their physiological failure, that includes heart fibrosis, electrical disturbances and peristaltic movement anomalies due to peripheral neuronal destruction along with heart microvascular platelet aggregation[8]. The genesis of the chronic inflammatory reaction is debatable. It may be induced by the persistence of the parasite in the tissues, due to an inadequate immune response or an exaggerated response as a result of missing regulatory mechanisms as an autoimmune disease[5]. Trypanocidal drug-treatment, during the chronic phase, diminishes the parasite load but was unable to revert or to halt the development of the cardiac pathology[9], arguing that myocardial damage may be independent of the parasite[10].

As mentioned above, IL-17 is crucial for the control of the acute infection[11,12]. Its over expression induces an earlier control of parasite replication and a massive, uncontrolled inflammatory reaction that kills the host[12]. These results are in agreement with the postulated role for IL-17 as an inflammatory cytokine[13-15]. On the other hand, there is evidence that IL-17 may regulate Th1 responses or recruits IL-10 neutrophil producers, favoring host survival during the acute infection by the down-regulation of an exacerbated immune response[5,16,17]. Experimental evidence concerning the role of IL-17 during the chronic phase of *T. cruzi* infection is missed. However, recently, two studies concerning the production and blood levels of IL-17 in Chagas patients have reported that subjects with cardiomyopathy have lower levels of IL-17 when compared with patients that were free of cardiac disease[18,19]. Therefore, in agreement with experimental studies, the authors claim that IL-17 was a disease-protective cytokine in the chronic *T. cruzi* infection. Also, they have proposed that higher levels of this interleukin would be a reliable biomarker for patients that do not present any clinical signs of myocardial disease, known as the indeterminate form of the chronic Chagas' disease[19]. High production of IL-17 is associated with some autoimmune and inflammatory diseases, and its blockade is usually beneficial[13]. Therefore, the protective role of IL-17 in the evolution of Chagas' disease is rather a surprising finding, considering its possible nature as an

Copyrights: © 2017 Mengel, J. This is an Open access article distributed under the terms of Creative Commons Attribution 4.0 International License.

autoimmune disease. Recently, TH-17 could not be associated with inflammatory but rather with a homeostatic/regulatory signature[20]. This observation would favor an alternative hypothesis, and one should consider different biological functions for TH-17, depending on the producer cell-type or even the location (organ) these cells are parked. However, Chagas' disease may include another particular situation since one of the most common drugs used to treat chagasic heart failure is digoxin, a drug reported to be a potent inhibitor of IL-17 production either in mice or humans[21]. Information about drugs taken by chagasic patients is missed from both clinical studies mentioned above.

Conclusion

In this opinion letter, we have briefly discussed the role of IL-17 in Chagas' disease, proposing an alternative explanation to the fact that this interleukin was diminished in chagasic patients with established heart disease, especially in patients with congestive heart failure[19]. We argue that lower levels of IL-17 could be due to the use of digoxin intake by patients rather than a particular immune response that could favor or not the production of IL-17. Therefore, an alternative interpretation of these results may well be considered, and further studies/information is needed to clarify this point.

Conflicts of interest: The authors declare no conflicts of interest.

REFERENCES

1. Gonzalez, F.B., Calmon, H.F., Fernández, B.R., et al. *Trypanosoma cruzi* Experimental Infection Impacts on the Thymic Regulatory T Cell Compartment. (2016) PLoS Negl Trop Dis 10(1): e0004285.
Pubmed | Crossref | Others

2. Koberle, F., Chagas' disease and Chagas' syndromes: the pathology of American trypanosomiasis (1968) Adv Parasitol 6: 63-116.
Pubmed | Crossref | Others

3. Albareda, M.C., Laucella, S.A., Alvarez, M.G., et al. *Trypanosoma cruzi* modulates the profile of memory CD8+ T cells in chronic Chagas' disease patients. (2006) Int Immunol 18(3): 465-471.
Pubmed | Crossref | Others

4. Cardillo, F., Cunha, F.Q., Tamashiro,W.M., et al. NK1.1+ cells and T-cell activation in euthymic and thymectomized C57Bl/6 mice during acute *Trypanosoma cruzi* infection. (2002) Scand J Immunol 55(1): 96-104.
Pubmed | Crossref | Others

5. Cardillo, F., de Pinho, R.T., Antas, P.R., et al. Immunity and immune modulation in *Trypanosoma cruzi* infection (2015) Pathog Dis 73(9): ftv082.
Pubmed | Crossref | Others

6. Cardillo, F., Voltarelli, J.C., Reed, S.G., et al. Regulation of *Trypanosoma cruzi* infection in mice by gamma interferon and interleukin 10: role of NK cells. (1996) Infect Immun 64(1): 128-134.
Pubmed | Crossref | Others

7. Cardillo, F., Postol, E., Nihei, J., et al. B cells modulate T cells so as to favour T helper type 1 and CD8+ T-cell responses in the acute phase of *Trypanosoma cruzi* infection. (2007) Immunology 122(4): 584-595.
Pubmed | Crossref | Others

8. Mengel, J.O., M.A. Rossi, Chronic chagasic myocarditis pathogenesis: dependence on autoimmune and microvascular factors. (1992) Am Heart J 124(4): 1052-1057.
Pubmed | Crossref | Others

9. Morillo, C.A., Marin-Neto, J.A., Avezum, A., et al., Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy (2015) N Engl J Med 373(14): 1295-1306.
Pubmed | Crossref | Others

10. Mengel, J., Cardillo, F., Pontes-de-Carvalho, L., et al. Chronic Chagas' Disease: Targeting the Interleukin-2 Axis and Regulatory T Cells in a Condition for Which There Is No Treatment. (2016) Front Microbiol 7: 675.
Pubmed | Crossref | Others

11. Miyazaki, Y., Hamano, S., Wang, S., et al. IL-17 is necessary for host protection against acute-phase *Trypanosoma cruzi* infection. J Immunol (2010) 185(2): 1150-1157.
Pubmed | Crossref | Others

12. Kitada, S., Kayama, H., Okuzaki, D., et al. BATF2 inhibits immunopathological Th17 responses by suppressing Il23a expression during *Trypanosoma cruzi* infection. (2017) J Exp Med 214(5): 1313-1331.
Pubmed | Crossref | Others

13. Kim, B.S., Park, Y.J., Chung, Y., et al. Targeting IL-17 in autoimmunity and inflammation. (2016) Arch Pharm Res 39(11): 1537-1547.
Pubmed | Crossref | Others

14. Paquissi, F.C., Immunity and Fibrogenesis: The Role of Th17/IL-17 Axis in HBV and HCV-induced Chronic Hepatitis and Progression to Cirrhosis. (2017) Front Immunol 8: 1195.
Pubmed | Crossref | Others

15. Robert, M., Miossec, P. Effects of Interleukin 17 on the cardiovascular system. (2017) Autoimmun Rev 16(9): 984-991.
Pubmed | Crossref | Others

16. Da Matta Guedes, P.M., Gutierrez, F.R., Maia, F.L., et al., IL-17 produced during *Trypanosoma cruzi* infection plays a central role in regulating parasite-induced myocarditis. (2010) PLoS Negl Trop Dis 4(2): e604.
Pubmed | Crossref | Others

17. Tosello Boari, J., Amezcua Vesely, M.C., Bermejo, D.A., et al. IL-17RA signaling reduces inflammation and mortality during *Trypanosoma cruzi* infection by recruiting suppressive IL-10-producing neutrophils. (2012) PLoS Pathog 8(4): e1002658.
Pubmed | Crossref | Others

18. Magalhaes, L.M., Villani, F.N., Nunes Mdo, C., et al. High interleukin 17 expression is correlated with better cardiac function in human Chagas disease. (2013) J Infect Dis 207(4): 661-665.
Pubmed | Crossref | Others

19. Sousa, G.R., Gomes, J.A., Damasio, M.P., et al. The role of interleukin 17-mediated immune response in Chagas disease: High level is correlated with better left ventricular function. (2017) PLoS One 12(3): e0172833.
Pubmed | Crossref | Others

20. Zhao, Q., Harbour, S.N., Kolde, R., et al. Selective Induction of Homeostatic Th17 Cells in the Murine Intestine by Cholera Toxin Interacting with the Microbiota. (2017) J Immunol 199(1): 312-322.
Pubmed | Crossref | Others

21. Huh, J.R., Leung, M.W., Huang, P., et al. Digoxin and its derivatives suppress TH17 cell differentiation by antagonizing RORgammat activity. (2011) Nature 472(7344): 486-490.
Pubmed | Crossref | Others