Jentashapir J Health Res. 2018 October; 9(5):e83541. doi: 10.5812/jjhs.83541.

Published online 2018 December 16. **Letter**

The Ambiguous Role of Treg Cells in *Mycobacterium tuberculosis* Pathogenesis

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Received 2018 August 22; **Accepted** 2018 September 10.

Keywords: Mycobacterium tuberculosis, T-Regulatory Cells, Tuberculosis, Microbial Pathogenesis

Dear Editor,

Tuberculosis is the second life-threatening infectious disease in the world, which is caused by *Mycobacterium tuberculosis* complex (MTBC). It is estimated almost 2 billion people are infected with *M. tuberculosis* (*Mtb*), with approximately 5 - 10% of this population being involved with the active form of tuberculosis. According to the World Health Organization (WHO) report in 2016, about 10.4 million new TB cases and 1.7 million deaths from TB occur around the worldwide (1, 2). Human immunodeficiency virus (HIV) plays an important role in susceptibility to tuberculosis. Among new TB cases in 2016, 0.4 million was also contaminated with HIV accounting for 40% of all TB cases (1-3).

Mtb is a facultative intracellular pathogen that is released to the atmosphere by sneezing, coughing, and aerosols of TB patients. When *Mtb* enters the lungs, it is bordered by alveolar macrophages that uptake *Mtb* antigens and act as Antigen Processing Cells (APCs), inducing a cellular immune system especially Th1 to produce IFN-γ, IL-2, and TNF-α for stopping *Mtb* replication phase and protective immunity against tuberculosis (4). Furthermore, Th2 cells produce IL-4, IgE, and IgG, which are involved in tuberculosis lesion. Given the literature, the complexities of various cytokines and interleukins in TB-infected lungs, particularly IL-4 and TNF-α, are responsible for the progression of fibrosis, decreasing Th1 activities, and downregulating the protective immune response combating *Mtb* (3, 5). In recent decades, the role of Treg cells in microbial pathogenesis has been focused by researchers and they have proposed contrary hypotheses about the role of Treg in tuberculosis pathogenesis.

The class of T regulatory cells (Treg cells) is one of the subsets of T-cells that lead to the suppressive immunity response to self-antigens, decreasing Th1 immunity reaction, a balance between immune system and recently, a role during infections (6). The fork-head winged helix family transcriptional repressor p3 (Foxp3) is an accurate indicator for production and synthesis of CD25 + CD4 + Treg cells in the human that can react with nuclear factor-kB (NF-kB) and decrease the expression of immune-cytokines including IL-2, IL-4, and IFN-γ, causing the decreased immune-protective response against infectious diseases (6, 7). Moreover, Treg cells can express a surface protein as CTLA-4. This surface protein can interact with CD80 and CD86, leading to the prevention of Th1 activation and progression of intracellular pathogens such as *Mycobacterium tuberculosis* (3, 7). Therefore, researchers declare that Treg cells can involve in tuberculosis pathogenesis by conducting several studies to determine the role of Treg cells in the progression of tuberculosis.

Nowadays, several reports show that T-regulatory cells increase in peripheral blood cell (PBC) specimens of TB-active patients although the number of Treg cells is normal or decreases in latent-TB infected (LTBI) individuals (8, 9). In addition, several studies proved increasing CD4 + CD25 + Foxp3 + Treg cells after BCG vaccination (10). Moreover, in some experiments, comparing the expression amount of the Foxp3 transcription factor between active and latent forms of tuberculosis, the expression of Foxp3 transcription factor was increased in active-TB patients (9). According to He et al., in some cases, Treg cells are not detected in blood samples because of migrating to the lung and accumulating in the site of infections (11). Sharma et al. showed the high expression of the Foxp3 factor in tuberculosis site of infection leading to the production of Treg cells around tuberculosis lesions (12). In contrast, sev-

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eral studies exist declaring that there is no significant difference in the expression amount of the Foxp3 transcription factor between active-TB patients and healthy individuals (3, 13). Furthermore, Burl et al. recently published a report indicating decreasing Foxp3 in newly TB-diagnosed patients (14). Ghazalsofala et al. reported the low expression of the Foxp3 factor in newly TB-diagnosed patients. They proposed that Treg cells are migrated to the lymph nodes, lung, and primary sites in initial stages in new-TB patients (3).

In summary, almost one-third of the population is infected with *M.tb* and 5 - 10% of these TB-infected people change to active TB. Various hypotheses are proposed to describe the reasons for this natural process. Treg cells are considered as one of the best candidates for this phenomenon but there are contrary results and confusing information about the role of T-regulatory cells in tuberculosis pathogenesis. It is essential to establish large experiments to obtain more information about the role of Treg cells among active-TB patients, latent-TB infected patients, treated TB-patients, and normal groups.

Footnotes

Conflict of Interest: None declared.

Funding/Support: None declared.

References

1. World Health Organization. *World malaria report 2015*. WHO; 2016.
2. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. *N Engl J Med*. 2002;**347**(23):1860–6. doi: 10.1056/NEJMcp021045. [PubMed: 12466511].
3. Ghazalsofala R, Rezaee SA, Rafatpanah H, Vakili R, Ghazvini K, Heidarnejad F, et al. Evaluation of CD4+ CD25+ FoxP3+ regulatory T cells and FoxP3 and CTLA-4 gene expression in patients with newly diagnosed tuberculosis in northeast of Iran. *Jundishapur J Microbiol*. 2015;**8**(4). e17726. doi: 10.5812/jjm.8(4)2015.17726. [PubMed: 26034548]. [PubMed Central: PMC4449857].
4. Karbalaei Zadeh Babaki M, Soleimanpour S, Rezaee SA. Antigen 85 complex as a powerful Mycobacterium tuberculosis immunogene: Biology, immune-pathogenicity, applications in diagnosis, and vaccine design. *Microb Pathog*. 2017;**112**:20–9. doi: 10.1016/j.micpath.2017.08.040. [PubMed: 28942172].
5. Lienhardt C, Azzurri A, Amedei A, Fielding K, Sillah J, Sow OY, et al. Active tuberculosis in Africa is associated with reduced Th1 and increased Th2 activity in vivo. *Eur J Immunol*. 2002;**32**(6):1605–13. doi: 10.1002/1521-4141(200206)32:6<1605::AID-IMMU1605>3.0.CO;2-6. [PubMed: 12115643].
6. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. *Nat Rev Immunol*. 2008;**8**(7):523–32. doi: 10.1038/nri2343. [PubMed: 18566595]. [PubMed Central: PMC2665249].
7. Tamura C, Nakazawa M, Kasahara M, Hotta C, Yoshinari M, Sato F, et al. Impaired function of dendritic cells in alymphoplasia (aly/aly) mice for expansion of CD25+CD4+ regulatory T cells. *Autoimmunity*. 2006;**39**(6):445–53. doi: 10.1080/08916930600833390. [PubMed: 17060023].
8. Shafiani S, Tucker-Heard G, Kariyone A, Takatsu K, Urdahl KB. Pathogen-specific regulatory T cells delay the arrival of effector T cells in the lung during early tuberculosis. *J Exp Med*. 2010;**207**(7):1409–20. doi: 10.1084/jem.20091885. [PubMed: 20547826]. [PubMed Central: PMC2901066].
9. Hougardy JM, Place S, Hildebrand M, Drowart A, Debrie AS, Locht C, et al. Regulatory T cells depress immune responses to protective antigens in active tuberculosis. *Am J Respir Crit Care Med*. 2007;**176**(4):409–16. doi: 10.1164/rccm.200701-084OC. [PubMed: 17541018].
10. Hanekom WA. The immune response to BCG vaccination of newborns. *Ann N Y Acad Sci*. 2005;**1062**:69–78. doi: 10.1196/annals.1358.010. [PubMed: 16461790].
11. He XY, Xiao L, Chen HB, Hao J, Li J, Wang YJ, et al. T regulatory cells and Th1/Th2 cytokines in peripheral blood from tuberculosis patients. *Eur J Clin Microbiol Infect Dis*. 2010;**29**(6):643–50. doi: 10.1007/s10096-010-0908-0. [PubMed: 20306324].
12. Sharma PK, Saha PK, Singh A, Sharma SK, Ghosh B, Mitra DK. FoxP3+ regulatory T cells suppress effector T-cell function at pathologic site in miliary tuberculosis. *Am J Respir Crit Care Med*. 2009;**179**(11):1061–70. doi: 10.1164/rccm.200804-529OC. [PubMed: 19246720].
13. Chiacchio T, Casetti R, Butera O, Vanini V, Carrara S, Girardi E, et al. Characterization of regulatory T cells identified as CD4(+)CD25(high)CD39(+) in patients with active tuberculosis. *Clin Exp Immunol*. 2009;**156**(3):463–70. doi: 10.1111/j.1365-2249.2009.03908.x. [PubMed: 19438599]. [PubMed Central: PMC2691975].
14. Burl S, Hill PC, Jeffries DJ, Holland MJ, Fox A, Lugos MD, et al. FOXP3 gene expression in a tuberculosis case contact study. *Clin Exp Immunol*. 2007;**149**(1):117–22. doi: 10.1111/j.1365-2249.2007.03399.x. [PubMed: 17465993]. [PubMed Central: PMC1942016].