



IFN- γ -, IL-4-, IL-17-, PD-1-Expressing T Cells and B Cells in Peripheral Blood from Tuberculosis Patients

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ABSTRACT

Although the efficacy of tuberculosis (TB) vaccines is tightly linked to cell-mediated immunity, some functions of T and B cells in TB patients remain unclear. To address how *Mycobacterium tuberculosis* infection inhibits T effector responses, we assessed the proportions of T cell subsets and B cells in peripheral blood from pulmonary TB (PTB) patients, pleural TB (PLTB) patients, and healthy subjects (HS, who showed purified protein derivative (PPD)-positive reactions) with flow cytometry. Compared to HS, PTB and PLTB patients exhibited higher proportions of B cells and Th17 cells, and lower proportions of Th2 cells and ratios of Th1 to Th17 cells and of Th2 to Th17 cells. PTB patients had higher CD4⁺ T cells and PD-1⁺ CD4⁺ T cells than HS. Newly diagnosed PTB patients (nPTB) had higher proportions of B cells than HS; in contrast, PTB patients subjected to effective treatments (oPTB) and HS shared similar proportions of B cells. oPTB patients had higher proportions of CD4⁺ T cells, Th17 cells, and PD-1⁺ CD4⁺ T cells than HS, but this difference did not occur in nPTB patients. These findings suggest that shifting ratios of Th1 to Th17 cells may be beneficial for *M. tuberculosis* to amplify.

KEYWORDS

Mycobacterium tuberculosis; B Cells; T Cells; Th Cells; PD-1

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References

- [1] World Health Organization, "Global Tuberculosis Control," WHO Report, 2010. <http://www.who.int/tb/publications/global-report/2010/en/index.html>
- [2] S. Gurunathan, D. M. Klinman and R. A. Seder, "DNA Vaccines: Immunology, Application, and Optimization," *Annual Review of Immunology*, Vol. 18, 2000, pp. 927-974. doi:10.1146/annurev.immunol.18.1.927
- [3] F. Abebe and G. Bjune, "The Protective Role of Antibody Responses during Mycobacterium tuberculosis Infection," *Clinical & Experimental Immunology*, Vol. 57, No. 2, 2009, pp. 235-243. doi:10.1111/j.1365-2249.2009.03967.x
- [4] U. Sester, M. Fousse, J. Dirks, U. Mack, A. Prasse, M. Singh, A. Lalvani and M. Sester, "Whole-Blood Flow-Cytometric Analysis of Antigen-Specific CD4 T-Cell Cytokine Profiles Distinguishes Active Tuberculosis from Non-Active States," *PLoS One*, Vol. 6, No. 3, 2011, Article ID: e17813. doi:10.1371/journal.pone.0017813
- [5] L. E. Harrington, R. D. Hatton, P. R. Mangan, H. Turner, T. L. Murphy, K. M. Murphy and C. T. Weaver, "Inter-leukin 17-Producing CD4⁺ Effector T Cells Develop via a Lineage Distinct from the T Helper Type 1 and 2 Lineages," *Nature Immunology*, Vol. 6, No. 11, 2005, pp. 1123-1132. doi:10.1038/ni1254

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- [6] R. I. Nurieva, Y. Chung, D. Hwang, X. O. Yang, H. S. Kang, L. Ma, Y. H. Wang, S. S. Watowich, A. M. Jetten, Q. Tian and C. Dong, " Generation of T Follicular Helper Cells Is Mediated by Interleukin-21 but Independent of T Helper 1, 2, or 17 Cell Lineages," *Immunity*, Vol. 29, No. 1, 2008, pp. 138-149. doi:10.1016/j.immuni.2008.05.009
- [7] D. Young and C. Dye, " The Development and Impact of Tuberculosis Vaccines," *Cell*, Vol. 124, No. 4, pp. 683-687. doi:10.1016/j.cell.2006.02.013
- [8] S. Bertholet, G. C. Ireton, M. Kahn, J. Guderian, R. Mohamath, N. Stride, E. M. Laughlin, S. L. Baldwin, T. S. Vedvick, R. N. Coler and S. G. Reed, " Identification of Human T Cell Antigens for the Development of Vaccines against Mycobacterium tuberculosis," *The Journal of Immunology*, Vol. 181, No. 11, 2008, pp. 7948-7957.
- [9] S. J. Aujla, P. J. Dubin and J. K. Kolls, " Th17 Cells and Mucosal Host Defense," *Seminars in Immunology*, Vol. 19, No. 6, 2007, pp. 377-382. doi:10.1016/j.smim.2007.10.009
- [10] E. Bettelli, T. Korn and V. K. Kuchroo, " Th17: The Third Member of the Effector T Cell Trilogy," *Current Opinion in Immunology*, Vol. 19, No. 6, 2007, pp. 652-657. doi:10.1016/j.coi.2007.07.020
- [11] S. A. Khader, G. K. Bell, J. E. Pearl, J. J. Fountain, J. Rangel-Moreno, G. E. Cilley, F. Shen, S. M. Eaton, S. L. Gaffen, S. L. Swain, R. M. Locksley, L. Haynes, T. D. Randall and A. M. Cooper, " IL-23 and IL-17 in the Establishment of Protective Pulmonary CD4+ T Cell Responses after Vaccination and during Mycobacterium tuberculosis Challenge," *Nature Immunology*, Vol. 8, No. 4, 2007, pp. 369-377.
- [12] S. A. Khader and A. M. Cooper, " IL-23 and IL-17 in Tuberculosis," *Cytokine*, Vol. 41, No. 2, 2008, pp. 79-83. doi:10.1016/j.cyto.2007.11.022
- [13] E. Torrado and A. M. Cooper, " IL-17 and Th17 Cells in Tuberculosis," *Cytokine & Growth Factor Reviews*, Vol. 21, No. 6, 2010, pp. 455-462. doi:10.1016/j.cytogfr.2010.10.004
- [14] T. R. Mosmann and R. L. Coffman, " TH1 and TH2 Cells: Different Patterns of Lymphokine Secretion Lead to Different Functional Properties," *Annual Review of Immunology*, Vol. 7, 1989, pp. 145-173. doi:10.1146/annurev.iy.07.040189.001045
- [15] G. T. Seah, G. M. Scott and G. A. Rook, " Type 2 Cytokine Gene Activation and Its Relationship to Extent of Disease in Patients with Tuberculosis," *Journal of Infectious Diseases*, Vol. 181, No. 1, 2000, pp. 385-389. doi:10.1086/315200
- [16] M. Kopf, G. Le Gros, A. J. Coyle, M. Kosco-Vilbois and F. Brombacher, " Immune Responses of IL-4, IL-5, IL-6 Deficient Mice," *Immunological Reviews*, Vol. 148, 1995, pp. 45-69. doi:10.1111/j.1600-065X.1995.tb00093.x
- [17] K. Shimoda, J. van Deursen, M. Y. Sangster, S. R. Sarawar, R. T. Carson, R. A. Tripp, C. Chu, F. W. Quelle, T. Nosaka, D. A. Vignali, P. C. Doherty, G. Grosveld, W. E. Paul and J. N. Ihle, " Lack of IL-4-Induced Th2 Response and IgE Class Switching in Mice with Disrupted Stat6 Gene," *Nature*, Vol. 380, No. 6575, 1996, pp. 630-633. doi:10.1038/380630a0
- [18] S. Crotty, " Follicular Helper CD4 T Cells (TFH)," *Annual Review of Immunology*, Vol. 29, 2011, pp. 621-663. doi:10.1146/annurev-immunol-031210-101400
- [19] E. K. Deenick and C. S. Ma, " The Regulation and Role of T Follicular Helper Cells in Immunity," *Immunology*, Vol. 134, No. 4, 2011, pp. 361-367. doi:10.1111/j.1365-2567.2011.03487.x
- [20] Y. Latchman, C. R. Wood, T. Chernova, D. Chaudhary, M. Borde, I. Chernova, Y. Iwai, A. J. Long, J. A. Brown, R. Nunes, E. A. Greenfield, K. Bourque, V. A. Boussiotis, L. L. Carter, B. M. Carreno, N. Malenkovich, H. Nishimura, T. Okazaki, T. Honjo, A. H. Sharpe and G. J. Freeman, " PD-L2 Is a Second Ligand for PD-1 and Inhibits T Cell Activation," *Nature Immunology*, Vol. 2, No. 3, 2001, pp. 261-268. doi:10.1038/85330
- [21] S. M. Mangan, L. C. Sandin, K. Anger, A. J. Korman, A. Loskog and T. H. Totterman, " Enhanced Tumor Eradication by Combining CTLA-4 or PD-1 Blockade with CpG Therapy," *Journal of Immunotherapy*, Vol. 33, No. 3, 2010, pp. 225-235.
- [22] A. H. Sharpe, E. J. Wherry, R. Ahmed and G. J. Freeman, " The Function of Programmed Cell Death 1 and Its Ligands in Regulating Autoimmunity and Infection," *Nature Immunology*, Vol. 8, No. 3, 2007, pp. 239-245. doi:10.1038/ni1443
- [23] S. Sakai, I. Kawamura, T. Okazaki, K. Tsuchiya, R. Uchiyama and M. Mitsuyama, " PD-1-PD-L1 Pathway Impairs T(h)1 Immune Response in the Late Stage of Infection with Mycobacterium bovis Bacillus Calmette-Guérin," *International Immunology*, Vol. 22, No. 12, pp. 915-925.

- [24] E. Lazar-Molnar, B. Chen, K. A. Sweeney, E. J. Wang, W. Liu, J. Lin, S. A. Porcelli, S. C. Almo, S. G. Nathanson and W. R. Jacobs Jr., " Programmed Death-1 (PD-1)-Deficient Mice Are Extraordinarily Sensitive to Tuberculosis," *Proceedings of the National Academy of Sciences USA*, Vol. 107, No. 30, 2010, pp. 13402-13407. doi:10.1073/pnas.1007394107
- [25] J. O. Jurado, I. B. Alvarez, V. Pasquinelli, G. J. Martínez, M. F. Quiroga, E. Abbate, R. M. Musella, H. E. Chuluyan and V. E. García, " Programmed Death (PD)-1: PD-Ligand 1/PD-Ligand 2 Pathway Inhibits T Cell Effector Functions during Human Tuberculosis," *Journal of Immunotherapy*, Vol. 181, No. 1, 2008, pp. 116-125.
- [26] X. Y. He, J. Li, J. Hao, H. B. Chen, Y. Z. Zhao, X. Y. Huang, K. He, L. Xiao, L. P. Ye, Y. M. Qu and L. H. Ge, " Assessment of Five Antigens from *Mycobacterium tuberculosis* for Serodiagnosis of Tuberculosis," *Clinical and Vaccine Immunology*, Vol. 18, No. 4, pp. 565-570. doi:10.1128/CVI.00507-10
- [27] S. Banerjee, A. Nandyala, R. Podili, V. M. Katoch, K. J. Murthy and S. E. Hasnain, " *Mycobacterium tuberculosis* (Mtb) Isocitrate Dehydrogenases Show Strong B Cell Response and Distinguish Vaccinated Controls from TB Patients," *Proceedings of the National Academy of Sciences USA*, Vol. 101, No. 34, 2004, pp. 12652-12657. doi:10.1073/pnas.0404347101
- [28] W. Barcelos, O. A. Martins-Filho, T. M. Guimaraes, M. H. Oliveira, S. Spindola-de-Miranda, B. N. Carvalho and P. Toledo Vde, " Peripheral Blood Mononuclear Cells Immunophenotyping in Pulmonary Tuberculosis Patients before and after Treatment," *Microbiology and Immunology*, Vol. 50, No. 8, 2006, pp. 597-605.
- [29] T. M. Wozniak, B. M. Saunders, A. A. Ryan and W. J. Britton, " *Mycobacterium bovis* BCG-Specific Th17 Cells Confer Partial Protection against *Mycobacterium tuberculosis* Infection in the Absence of Gamma Interferon," *Infection and Immunity*, Vol. 78, No. 10, 2010, pp. 4187-4194. doi:10.1128/IAI.01392-09
- [30] J. Winek, U. Demkow, E. Rowińska-Zakrzewska, M. Szołkowska, M. Filewska, J. Jagodziński and K. Roszkowski-Sliz, " Comparison of Th1 and Th2 Response in the Blood of Tuberculous Patients and Healthy Contacts," *Pneumologia Alergologia Polska*, Vol. 77, No. 5, 2009, pp. 446-452.
- [31] V. H. Sai Priya, G. S. Latha, S. E. Hasnain, K. J. Murthy and V. L. Valluri, " Enhanced T Cell Responsiveness to *Mycobacterium bovis* BCG r32-kDa Ag Correlates with Successful Anti-Tuberculosis Treatment in Humans," *Cytokine*, Vol. 52, No. 3, pp. 190-193. doi:10.1016/j.cyto.2010.07.001
- [32] Y. Tsukamoto, M. Endoh, T. Mukai, Y. Maeda, T. Tamura, M. Kai and M. Makino, " Immunostimulatory Activity of Major Membrane Protein II from *Mycobacterium tuberculosis*," *Clinical and Vaccine Immunology*, Vol. 18, No. 2, 2010, pp. 235-242. doi:10.1128/CVI.00459-10
- [33] C. M. Rueda, N. D. Marín, L. F. García and M. Rojas, " Characterization of CD4 and CD8 T Cells Producing IFN- γ in Human Latent and Active Tuberculosis," *Tuberculosis (Edinburgh)*, Vol. 90, No. 6, 2010, pp. 346-353. doi:10.1016/j.tube.2010.09.003
- [34] A. M. Gallegos, J. W. J. van Heijst, M. Samstein, X. Su, E. G. Pamer and M. S. Glickman, " A Gamma Interferon Independent Mechanism of CD4 T Cell Mediated Control of *M. tuberculosis* Infection in Vivo," *PLOS Pathogens*, Vol. 7, No. 5, 2011, Article ID: e1002052. doi:10.1371/journal.ppat.1002052
- [35] S. C. de Cassan, A. A. Pathan, C. R. Sander, A. Minassian, R. Rowland, A. V. Hill, H. McShane and H. A. Fletcher, " Investigating the Induction of Vaccine-Induced Th17 and Regulatory T Cells in Healthy, *Mycobacterium bovis* BCG-Immunized Adults Vaccinated with a New Tuberculosis Vaccine, MVA85A," *Clinical and Vaccine Immunology*, Vol. 17, No. 7, 2010, pp. 1066-1073. doi:10.1128/CVI.00047-10
- [36] D. Freches, M. Romano, H. Korf, J. C. Renauld, J. Van Snick, C. Uyttenhove and K. Huygen, " Increased Pulmonary Tumor Necrosis Factor Alpha, Interleukin-6 (IL-6), and IL-17A Responses Compensate for Decreased Gamma Interferon Production in Anti-IL-12 Autovaccine-Treated, *Mycobacterium bovis* BCG-Vaccinated Mice," *Clinical and Vaccine Immunology*, Vol. 18, No. 1, 2011, pp. 95-104. doi:10.1128/CVI.00352-10
- [37] J. I. Basile, L. J. Geffner, M. M. Romero, L. Balboa, Y. García. C. Sabio, V. Ritacco, A. García, M. Cuffré, E. Abbate, B. López, L. Barrera, M. Ambroggi, M. Alemán, M. C. Sasiain and S. S. de la Barrera, " Outbreaks of *Mycobacterium tuberculosis* MDR Strains Induce High IL-17 T-Cell Response in Patients with MDR Tuberculosis That Is Closely Associated with High Antigen Load," *The Journal of Infectious Diseases*, Vol. 204, No. 7, 2011, pp. 1054-1064. doi:10.1093/infdis/jir460

- [38] T. Wang, M. Lv, Q. Qian, Y. Nie, L. Yu and Y. Hou, " Increased Frequencies of T Helper Type 17 Cells in Tuberculous Pleural Effusion," *Tuberculosis (Edinburgh)*, Vol. 91, No. 3, 2011, pp. 231-237. doi:10.1016/j.tube.2011.02.002
- [39] X. Chen, M. Zhang, M. Liao, M. W. Graner, C. Wu, Q. Yang, H. Liu and B. Zhou, " Reduced Th17 Response in Patients with Tuberculosis Correlates with IL-6R Expression on CD4+ T Cells," *American Journal of Respiratory and Critical Care Medicine*, Vol. 181, No. 7, 2009, pp. 734-742. doi:10.1164/rccm.200909-1463OC
- [40] A. Kahnert, P. Seiler, M. Stein, S. Bandermann, K. Hahnke, H. Mollenkopf and S. H. Kaufmann, " Alternative Activation Deprives Macrophages of a Coordinated Defense Program to Mycobacterium tuberculosis," *European Journal of Immunology*, Vol. 36, No. 3, 2006, pp. 631-647. doi:10.1002/eji.200535496
- [41] C. S. Hirsch, Z. Toossi, C. Othieno, J. L. Johnson, S. K. Schwander, S. Robertson, R. S. Wallis, K. Edmonds, A. Okwera, R. Mugerwa, P. Peters and J. J. Ellner, " Depressed T-cell Interferon-Gamma Responses in Pulmonary tuberculosis: Analysis of Underlying Mechanisms and Modulation with Therapy," *The Journal of Infectious Diseases*, Vol. 180, No. 6, 1999, pp. 2069-2073. doi:10.1086/315114
- [42] C. Lienhardt, A. Azzurri, A. Amedei, K. Fielding, J. Sillah, O. Y. Sow, B. Bah, M. Benagiano, A. Diallo, R. Manetti, K. Manneh, P. Gustafson, S. Bennett, M. M. D'Elios, K. McAdam and G. Del Prete, " Active Tuberculosis in Africa Is Associated with Reduced Th1 and Increased Th2 Activity in Vivo," *European Journal of Immunology*, Vol. 32, No. 6, 2002, pp. 1605-1613. doi:10.1002/1521-4141(200206)32:6<1605::AID-IMMU1605>3.0.CO;2-6
- [43] R. J. Al-Attayah and A. S. Mustafa, " Mycobacterial Antigen-Induced T Helper Type 1 (Th1) and Th2 Reactivity of Peripheral Blood Mononuclear Cells from Diabetic and non-Diabetic Tuberculosis Patients and Mycobacterium bovis Bacilli Calmette-Guérin (BCG)-Vaccinated Healthy Subjects," *Clinical & Experimental Immunology*, Vol. 158, No. 1, 2009, pp. 64-73. doi:10.1111/j.1365-2249.2009.04000.x
- [44] I. B. Alvarez, V. Pasquinelli, J. O. Jurado, E. Abbate, R. M. Musella, S. S. de la Barrera and V. E. Garcia, " Role Played by the Programmed Death-1-Programmed Death Ligand Pathway during Innate