Mycobacterium Tuberculosis Infection: Participation of TH1, TH2, TH17 and Regulatory T Cells in the Immune Response

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Abstract- Mycobacterium tuberculosis, the etiologic agent of Tuberculosis, is a pathogen that is widely distributed geographically. Tuberculosis is classified as a granulomatous inflammatory condition where effector cells accumulate at the site of mycobacterial infection to form the characteristic tubercle. Regulating proteins of Th1 and Th17 cells participate in the formation of Mycobacterium-induced granuloma. The predominance of Th2 phenotype cytokines increases the severity of Tuberculosis. Treg cells are increased in patients with active Tuberculosis but decrease with anti-Tuberculosis treatment. The increment of these cells causes down-regulation of adaptive immune response facilitating the persistence of the bacterial infection. Mycobacterium tuberculosis-induced Treg cells to secrete cytokines that inhibit the immune response. This has been considered an important evasion mechanism although it is not the only that intervenes. The evolution of the Mycobacterium tuberculosis infection will depend on the cytokines' network that traduces pathological change in cells and tissues which explain the clinical manifestations existing in affected patients.

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Introduction

Tuberculosis (TB) is one of the leading causes of mortality and morbidity in different age groups throughout the world, especially in developing countries. TB is classified as a granulomatous inflammatory condition where effector cells accumulate at the site of mycobacterial infection to form the characteristic tubercle. Bacterial virulence factors, nutritional state, host genetic condition, and immune response play an important role in the evolution of the infection (1). Mycobacterium tuberculosis (Mtb) enters the body by the airway (95%). It is usually located in the lungs, TB, but can spread through the blood and it produces extrapulmonary tuberculosis, with the involvement of the lymph nodes, pleura, genitourinary system, meninges, and peritoneum. Ninety percent of infected individuals will remain latently infected without clinical symptom, however, 10% of the individuals infected with Mtb will develop the active disease (2).

Mycobacteria persistence is associated with failure in the immune vigilance and reactivation of the disease among other factors. Many cells such as neutrophils, macrophages, dendritic cells, B-Lymphocytes, and NK cells take place in the immune response in the Mtb infection. The cytokines that are secreted from these cells form a complex network that traduces pathological change in cells and tissues.

The genetically diverse Mtb strains from different lineages have been shown to induce variable immune system response. The establishment of the infection determines, with the time of evolution, the development of the active and latent forms (1). We discuss the factors related to immune response and the participation of cells and regulating proteins in the Mtb infection. Furthermore, overall information inherent to the behavior of cytokines

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that allow explaining the clinical manifestations and the evolution of the disease among other aspects, that represents a substantial contribution to the knowledge of TB will be discussed.

Immune response: Participation of Th1, Th2, Th17, and regulatory T cells

Innate and adaptive immune responses are important for the eradication of the microorganism. Armed effector T cells are crucial to almost all adaptive immune response. Alterations of the T helper cells functions conduce to inefficient clearance of pathogens and can cause inflammation and autoimmunity (3). The reasons for the impaired Mtb-specific T cell function in active tuberculosis remain controversial. When mutations in Th-1 cytokine signaling pathways (Interferon-γ and Interleukin-12) are present, the patients are susceptible to overwhelming infection with Mtb (4,5). IFN-γ is a critical mediator of macrophage activation and bactericidal mechanisms. Impaired Th1 lymphocyte response in HIV infection also produces ineffective immunity to Mtb. Latent TB infection, reactivation and advanced TB are associated with predominance of Th2 cytokines (Interleukin-4 and interleukin-10) (6-8).

Patients with extrapulmonary disease have immune responses in vitro suggestive of Th1 response, whereas patients with the military/disseminated disease have a suggestive Th2 response (9). Observations appoint that virulent Mtb strains preferentially induce Th2 cytokines expression, whereas less virulent strains induce Th1 cytokines, including interferon-γ and tumor necrosis factor-α (10-12). Overexpression of Th2 cytokines increases the severity of TB.

The etiological agent and its immunogenicity, evasion mechanisms of the pathogen, concurrent infections and infestations, the host genetic condition and the sufficiency or insufficiency of the immune system, are factors that can change the immune response in different pathological entities such as Helicobacter pylori and Mycobacterium tuberculosis infection among others (1,13). Coincident hookworm infection exerts a profound inhibitory effect on protective Th1 and Th17 response in latent TB and may predispose toward the development of active TB in humans (14).

In the antigenic presentation, the function of MHC class II molecules is to present peptides generated in the intracellular vesicles of B cells, macrophages, and other antigen-presenting cells to CD4 T cells. CD4+T cells are required for the control of intracellular Mtb. There is no doubt that immunity to Mtb depends on Th1-cell activity (Interferon-γ and Interleukin-12 and the production of tumor necrosis factor- α, but Th1 immunity alone is not sufficient to protect the host from Mtb infection, development of the disease, or dissemination (15). For other authors, active TB is characterized by a profound and prolonged suppression of Mtb-specific T cell responses, as evidenced by the decreased production of the Th1 phenotype cytokines as interleukin-2 and interferon-γ (16-20).

Incremented secretion of immunosuppressive cytokines (interleukin-10 and transforming growth factor-β) by mononuclear phagocytes has been implicated in decreased T cell function during TB (21-24). Other studies are controversial with respect to Interferon-γ serum levels. These studies reported significantly higher active TB levels in patients after treatment than in patients during anti- TB therapy, patients with history of TB contact and in healthy control Also, they observed the increment of interleukin-10, Interleukin-6, and decrease of Interleukin-4 (24,25).

The predominance of Th1 phenotype plays a relevant role in immunity to TB in children. The children are more prone to developing extrapulmonary manifestations of TB than adults. Pediatric TB is characterized by diminished Th1, Th2, and 17 phenotype cytokines, which favor the development of neurologic TB, suggesting a crucial role for these cytokines in protection against pediatric tuberculosis. Among children with extrapulmonary TB, those with neurologic involvement exhibited a more significantly diminished Ag-driven Interferon-γ and Interleukin-17 production (26).

Regulatory T cells (Treg) are implicated in the pathogenesis of Mtb infection. The induced Treg cells (iTreg) are differentiated from naïve T cells in the presence of Transforming growth factor β following T cell receptor (TCR) stimulation. These cells produce large amounts of Interleukin-10 and Transforming growth factor-β (27,28). Unlike Th1, Th2 or Th17 cells, iTreg displays immune-suppressive activity with minimal antigen specificity (28). Tregs are increased in the peripheral blood of active TB patients compared with M. bovis BCG vaccinated healthy donors. This agrees with recent reports in humans (30) and in the murine TB model (31,32). It has been demonstrated that Treg cells proliferate and accumulate at sites of infection and have the capacity to suppress immune responses (32). Circulating Treg cells in the peripheral blood declined progressively by anti-TB treatment (33). During the initial T cell response to Mtb infection, the pathogen induces the expansions of Treg cells that delay the onset of adaptive immunity, suggesting that Mtb has sequestered Treg to allow the bacterium replicate

endlessly in the lungs until T cells finally arrive. The induction of Treg by Mtb can be an evasive mechanism of the bacterium that permits its replication (34). The increase of these cells causes down-regulation of adaptive immune response facilitating the persistence of bacterial infections (34,35). Studies have appreciated high levels of circulating Treg cells in active TB infection which inhibit the Th1 response but not the Th17, facilitating the bacterial replication and tissue damage.

The presence of persisting immune activation and high frequencies of Treg lymphocytes may reflect immune dysregulation that predisposes individuals to clinical tuberculosis, specifically to extrapulmonary TB (36,37). There are high levels of transforming growth factor-β that produce active immunosuppression at the local infection site. These results suggest that an imbalance in the proportion of effector T cells to Treg cells, at the site of infection, may contribute to the establishment of TB infection (38). CD4, CD8, and γδ T- and B-lymphocytes among other cells produce their own complement of chemokines and cytokines, which amplify cellular recruitment and remodeling of the infection site into the granuloma.

Persistent TNF-α production is required to sustain the chemokine gradient and maintain the structure of the granuloma (39). Mtb has many strategies to evade the immune response and to survive within the macrophage in a bacterial-immunological equilibrium. Mtb manipulates different elements of immunity system during "establishment, maintenance and necrotic liquefaction of the granuloma facilitating transmission" and alters the host cell cycle to promote long-term persistence (40).

There are many factors that can change the immune response in different pathologies, such as: the etiological agent and its immunogenicity, evasion mechanisms of the pathogen, the type of pathology, the phase of the clinical entity, concurrent infections and infestations, the host genetic condition and the sufficiency or insufficiency of the immune system among others (1,13). All this determine the contradictions of some studies due to the quantity of variables that influence the immune system. The infection by Mtb does not escape all of the pointed considerations (13).

Genetic susceptibility to tuberculosis

Substantial evidence now exists regarding the human genetic contribution to susceptibility to tuberculosis. This evidence has come from several whole-genome linkage scans and numerous case-control association studies where the candidate genes were derived from the genome screens, animal models and hypotheses pertaining to the disease pathways. Human factors governing whether the infected individual will progress to active tuberculosis disease or not are usually assumed to be those governing the immunological state of the host, which are generally determined by the host's genetic makeup (41,42). Several studies to date have proven that genetic factors contribute to the outcome of tuberculosis, with an estimated heritability ranging from 36% to 80% (43,44,45,46,47).

Tuberculosis disease in a family does not follow a Mendelian pattern and is polygenic and multifactorial. Genetic susceptibility studies in tuberculosis are additionally complicated by the presence of two different genomes, the bacterium, and the host, and the influence their interaction can have on the disease (48).

Numerous studies have identified mostly in genes that are vital for immunity against intracellular pathogens in the interleukin (IL)-12/IL-23/interferon Interferon-γ axis (49). Several studies regarding the role of immune system-related genes have been performed. The human leucocyte antigen (HLA) region consists of approximately 200 genes that it has been postulated to affect infectious disease (50). HLA genes have been examined in several tuberculosis susceptibility studies and were some of the first genes to be investigated and associated with the disease. The HLA-DR2 is most consistently associated with TB in several populations such as India (51,52,53,54,55). It was found that the HLA-DQB10503 influence the progression of TB in the Cambodian population (56), whereas the DQB10601 was associated with TB in the Thai and South Indian population (52,53). DRB11302 was associated with TB susceptibility in a Venda population (50).

NRAMP1 is a divalent transporter localized to the late endosomal membrane that regulates cytoplasmic cation levels by specifically regulating the iron metabolism in the macrophages, leading to the possible containment of early mycobacterial infections (57). Genetic variants of NRAMP1 have been associated with TB in several studies (58,59,60), leading to the meta-analysis of NRAMP1 polymorphisms, which confirmed their involvement in TB susceptibility (60).

The Interferon-γ pathway is one of the most well known in TB because it is a flagship Th1 cytokine and plays a vital role in the protective immune response against Mtb infection (61). Several polymorphisms have been identified in Interferon-γ and in the alpha and beta chains of the Interferon-γ receptor (IFNGR) gene that was mapped to chromosome 12 and 6, respectively (62,63). The functional Interferon-γ and IFNGR form a vital complex essential for containing Mtb (62) One of the

most studied polymorphisms in Interferon-γ is located in the first intron (1874 T/A) and has been associated with TB susceptibility in several populations such as Spanish (64,65,66).

The nitric oxide synthase 2A gene (NOS2A) is induced in response to infections and cytokines and produces the inducible nitric oxide synthase protein (67). Among its other biological functions, nitric oxide (NO) has been recognized as a mediator of immunity to TB (68). The specific mechanism by which NO controls Mtb is not clear, but may involve disruption of bacterial DNA, proteins, signaling and/or induction of apoptosis of macrophages that contain the bacterium (69). It may also play a role in the formation of protective granulomas (70). Two SNPs (rs2779249 and rs2301369) in the promoter of NOS2A were associated with TB in a family-based study in 92 Brazilian families. NOS2A microsatellite promoter polymorphism was associated with TB in Colombia (71) and in the South African colored population.

Chemokines play an important role in the development of immune responses against tuberculosis. The C-C chemokine ligand-2 gene (CCL2) encodes monocyte chemoattractant protein-1 (MCP-1), which is essential for the recruitment of monocytes, T lymphocytes (72), and natural killer cells (73) to the site of mycobacterial infection. It may also take part in the localization of TB in the lungs by contributing to granuloma formation (72) and possibly have a role in T cell differentiation (74). The functional CCL2 promoter polymorphism rs1024611 (75) was associated with increased susceptibility to pulmonary TB in Mexicans and in Koreans (76). However, this polymorphism was not associated with TB in a smaller study of Brazilians (77) or in a large case-control association study in the South African colored population (78).

The family of mammalian Toll-like receptors (TLRs) consists of at least 13 proteins, each with a distinct function, which initiates the innate immune response. TLRs are central components of the innate immune response to mycobacterial infection (79,80)) and act as part of the pattern recognition system to signal the presence of Mtb in the host (81). Two common nonsynonymous polymorphisms in TLR1, namely rs4833095 (N248S) and rs5743618 (I602S), have been implicated in TB susceptibility in the African–American population (82). The rs5743708 SNP (Arg753Gln) was investigated in Turkey, and it was suggested that it might contribute to the risk of developing tuberculosis (83).

The gene encoding the collectin mannose-binding lectin (MBL) or mannose-binding protein (MBP) maps to chromosome 10. MBL is a serum lectin that acts as an opsonin to promote phagocytosis and modulates inflammation (84,85), and the variant alleles have been associated with protection against tuberculosis and particularly tuberculous meningitis in South Africa and Turkey (86,87,88). The transmembrane C-type lectin, dendritic cell-specific intracellular adhesion molecule (ICAM)-grabbing nonintegrin (DC-SIGN), or CD209, located on chromosome 19, is known to be the major M. tuberculosis receptor in human dendritic cells, and as such, functions in the pulmonary innate immune system (89). Two promoter variants, 871 A/G and 336 A/G, have been studied regarding susceptibility to tuberculosis in South Africa and the 871G/ 336A haplotype is significantly more frequent among healthy controls (90).

The vitamin D receptor gene (VDR) mediates the effects of the active metabolite of vitamin D, 1,25-dihydroxyvitamin D3, which suppresses the growth of Mtb in vitro (91,92) by stimulating cell-mediated immunity and activating monocytes (93). Conflicting results have been found in studies of VDR in TB (95,96). A recent study in South Africans determined that the ApaI 'AA' genotype and 'T'-containing TaqI genotypes predicted a faster response to TB treatment but did not detect an association with TB in a case-control analysis (97).

T cells in active and non-active tuberculosis

Early diagnosis of active TB followed by short-term anti-TB treatment remains a major strategy for TB control. The detection of the pathogen and Interferon-gamma (IFN-γ) release assays (IGRAs) for immune-diagnosis of its infection have been developed as the most important achievements over decades and are increasingly applied (98). IGRAs have no issues in sample preparation but cannot distinguish active TB from latent TB (LTB). This is a major defect that limits its clinical application because the treatments for active TB are considerably different from those of LTBI. Several additional markers have been explored to work in combination with IFN-γ, and some have produced considerable diagnostic improvements (99,100,101).

CD161-expressing T cells-indices are useful to discriminate active TB from LTB. Besides CD4 and CD8 (101,102), the immunological markers implicated in identification of active TB also include CD38, CD26, CD27, CD64 and CD161 (99,100,103,104). CD161 is a C-type lectin-like receptor expressed by a broad range of lymphocytes, including CD4+, CD8+, γδ+ T-cells, NK cells, and mucosal-associated invariant T (MAIT) cells. Consistent with the extraordinary heterogeneity of CD161-expressing cells, the biological functions of the

marker including its roles in mycobacterial infections are not well understood. Nevertheless, the decrease of CD161-expressing CD4 T cells in active TB patients was in line with the suppressed Th17 responses in the disease (105,106,107), in which, Th17 cells were CD161-positive (106,107). MAIT cells (CD161 positive) represent the most abundant innate-like T-cell population within the human body, comprising up to ~5% of the total T-cell population and are involved in anti-bacterial immunity (108).

Recently, it was shown that patients with active tuberculosis had significantly lower percentage of CD161-expressing CD8+TRAV1–2+ MAIT cells than those of uninfected and LTB subjects (109,110). This evidence suggest that CD161-expressing lymphocytes are important for protective immunity in preventing the progression of active TB from Mtb infection.

Studies reveal that cytokines' network is formed with the participation of the regulating proteins and different subset of cells to achieve control, persistence, and severity of TB. The synergistic, antagonistic, redundant and pleiotropic biological effects of regulating proteins can affect or not the immune response against Mtb. There is no doubt that immunity to Mtb depends on Th1-cell activity (IFN-γ and IL-12 and the production of TNF-α), but Th1 immunity alone is not sufficient to protect the host from Mtb infection, development of the disease, or dissemination. The predominance of Th2 phenotype cytokines (Interleukin-10 and Transforming growth factor β) increases the severity of TB. Treg cells that secrete immunosuppressive cytokines are increased in patients with active TB but decrease with anti-TB treatment. Mbt is considered a manipulator of protective immunity. The balance between host immunity and bacterial evasion strategies among other factors determine the control in vivo of Mtb. The intricate complexity of cytokines and chemokines stimulate the search for more effective therapeutics that permit the eradication of a disease such as TB.

The human factors governing whether the infected individual will progress to active TB disease or not are usually assumed to be those governing the immunological state of the host, which are generally determined by the host's genetic makeup, for example, genetic variants of NRAMP1 have been associated with TB, because that specifically regulate the iron metabolism in the macrophages, leading to possible containment of early mycobacterial, involvement in TB susceptibility, also the IFN-γ pathway is one of the most well known in TB because it is a flagship Th1 cytokine and plays a vital role in the protective immune response against Mtb infection. Several polymorphisms have been identified in IFNG and in the a and b chains of the IFN-γ receptor gene that was mapped to chromosome 12 and 6.

The detection of the pathogen, and IFN-γ release assays for immune-diagnosis of its infection, have been developed as the most important achievements over decades and are increasingly applied, IGRAs have no issues in sample preparation but cannot distinguish active TB from latent TB (LTB), the immunological markers implicated in identification of active TB include CD161, CD38, CD26, CD27, and CD64.

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References

1. Romero Adrián TB, Leal Montiel J, Fernández G, Valecillo A. Role of cytokines and other factors involved in the Mycobacterium tuberculosis infection. World J Immunol 2015;27:16-50.
2. Frieden TR, Sterling TR, Munsiff SS. Tuberculosis. Lancet 2003;362:887-99.
3. Wan YY, Flavell RA. How diverse- CD4 effector Tcells and their functions. J Mol Cell Biol 2009;1:20-36.
4. Martínez-Morales MC, Deswarte C, Castañeda-Casimiro J, Bustamante J, Blancas-Galicia L, Scheffler-Mendoza S. Disseminated infection by M.tuberculosis complex in patient with IFN-γ receptor 1 complete deficiency. Rev Alerg Mex 2017;64:499-504.
5. Sasindran SJ, Torrelles JB. Mycobacterium Tuberculosis Infection and Inflammation: what is Beneficial for the Host and for the Bacterium? Front Microbiol 2011;2:2.
6. Moreira-Teixeira L, Sousa J, McNab FW, Torrado E, Cardoso F, Machado H, et al. Type I IFN Inhibits Alternative Macrophage Activation during Mycobacterium tuberculosis Infection and Leads to Enhanced Protection in the Absence of IFN-γ Signaling. J Immunol Author Choice 2016;197:4714-26.
7. Bell LCK, Pollara G, Pascoe M, Tomlinson GS, Rannakoe J, Roe J, et al. In Vivo Molecular Dissection of the Effects of HIV-1 in Active Tuberculosis. PLoS Pathogens 2016;12:e1005469.
8. Senait Ashenafi, Getachew Aderaye, Amsalu Bekele,

Martha Zewdie, Getachew Aseffa, Anh Thu Nguyen Hoang, et al. Progression of clinical tuberculosis is associated with a Th2 immune response signature in combination with elevated levels of SOCS3. Clin Immunol 2014;15:84-8.

9. Amelio P, Portevin D, Reither K, Mhimbira F, Mpina M, Tumbo A, et al. Mixed Th1 and Th2 Mycobacterium tuberculosis-specific CD4 T cell responses in patients with active pulmonary tuberculosis from Tanzania. PLoS Negl Trop Dis 2017;11:e0005817.
10. Freeman S, Post FA, Bekker LG, Harbacheuski R, Steyn LM, Ryffel B, et al. Mycobacterium tuberculosis H37Ra and H37Rv differential growth and cytokine/chemokine induction in murine macrophages in vitro. J Interferon Cytokine Res 2006;26:27-33.
11. Surewicz K, Aung H, Kanost RA, Jones L, Hejal R, Toossi Z. The differential interaction of p38 MAP kinase and tumor necrosis factor-alpha in human alveolar macrophages and monocytes induced by Mycobacterium tuberculosis. Cell Immunol 2004;228:34-41.
12. Sun YJ, Lim TK, Ong AK, Ho BC, Seah GT, Paton NI. Tuberculosis associated with Mycobacterium tuberculosis Beijing and non-Beijing genotypes: a clinical and immunological comparison. BMC Infect Dis 2006;6:105.
13. Romero Adrián TB, Leal Montiel J, Monsalve-Castillo F, Mengual Moreno E, Ernesto García, McGregor E, et al. Helicobacter pylori: Bacterial factors and the role of cytokines in the immune response. Curr Microbiol 2010;60:143-55.
14. George PJ, Anuradha R, Kumaran PP, Chandrasekaran V, Nutman TB, Babu S. Modulation of mycobacterial-specific Th1 and Th17 cells in latent tuberculosis by coincident hookworm infection. J Immunol 2013;190:5161-8.
15. Zuñiga J, Torres García D, Santos Mendoza T, Rodríguez Reyna TS, Granados J, Yunis EJ. Cellular and humoral mechanisms involved in the control of tuberculosis. Clin Dev Immunol 2012;2012:193923.
16. Wang F, Mao L, Hou H, Wu S, Huang M, Yin B, et al. The source of Mycobacterium tuberculosis-specific IFN-γ production in peripheral blood mononuclear cells of TB patients. Int Immunopharmacol 2016;32:39-45.
17. Pollock KM, Montamat-Sicotte DJ, Grass L, Cooke GS, Kapembwa MS, Kon OM, et al. PD-1 Expression and Cytokine Secretion Profiles of Mycobacterium tuberculosis-Specific CD4+ T-Cell Subsets; Potential Correlates of Containment in HIV-TB Co-Infection. PLoS One 2016;11:e0146905.
18. Winslow GM, Cooper A, Reiley W, Chatterjee M, Woodland DL. Early T-cell responses in tuberculosis immunity. Immunol Rev 2008;225:10.
19. Herzmann C, Ernst M, Ehlers S, Stenger S, Maertzdorf J, Sotgiu G, Lange C. Increased frequencies of pulmonary regulatory T-cells in latent Mycobacterium tuberculosis infection. Eur Respir J 2012;40:1450-7.
20. Ribeiro-Rodrigues R, Resende CoT, Rojas R, Toossi Z, Dietze R, Boomet WH, et al. A role for CD4+CD25+ T cells in regulation of the immune response during human tuberculosis. Clin Exp Immunol 2006;144:25-34.
21. Diniz LM, Zandonade E, Dietze R, Pereira FE, Ribeiro-Rodrigues R. Short report: do intestinal nematodes increase the risk for multibacillary leprosy? Am J Trop Med Hyg 2001;65:852-4.
22. Arango Duque G, Descoteaux A. Macrophage Cytokines: Involvement in Immunity and Infectious Diseases. Front Immunol 2014;5:491.
23. Pinheiro RO, de Oliveira EB, Dos Santos G, Sperandio da Silva GM, de Andrade Silva BJ, et al. Immunosuppressive mechanisms in multi-drug-resistant tuberculosis and non-tuberculous mycobacteria patients. Clin Exp Immunol 2013;171:210-9.
24. Hossain MM, Norazmi M-N. Pattern Recognition Receptors and Cytokines in Mycobacterium tuberculosis Infection-The Double-Edged Sword? Biomed Res Int 2013;2013:179174.
25. Redford PS, Murray PJ, O'Garra A. The role of IL-10 in immune regulation during M. tuberculosis infection. Mucosal Immunol 2011;4:261-70.
26. Kumar NP, Anuradha R, Suresh R, Ganesh R, Shankar J, Kumaraswami V. Suppressed type 1, type 2, and type 17 cytokine responses in active tuberculosis in children. Clin Vaccine Immunol 2011;18:1856-64.
27. Weiner HL. Induction and mechanism of action of transforming growth factor-β-secreting Th3 regulatory cells. Immunol Rev 2001;182:207-14.
28. Vieira PL, Christensen JR, Minaee S, O'Neill EJ, Barrat FJ, Boonstra A, et al. IL-10-secreting regulatory T cells do not express Foxp3 but have comparable regulatory function to naturally occurring CD4 + CD25+ regulatory T cells. J Immunol 2004;172:5986-93.
29. Singh A, Dey AB, Mohan A, Sharma PK, Mitra DK. Foxp3+ Regulatory T Cells among Tuberculosis Patients: Impact on Prognosis and Restoration of Antigen Specific IFN-γ Producing T Cells. PLoS One 2012;7:e44728.
30. Quinn KM, McHugh RS, Rich FH, Goldsack LM, de Lisle GW, Buddle BM, et al. Inactivation of CD4+ CD25+ regulatory T cells during early mycobacterial infection increases cytokine production but does not affect pathogen load. Immunol Cell Bio 2006;184:467-74.
31. Scott-Browne JP, Shafiani S, Tucker-Heard G, Ishida-Tsubota K, Fontenot DJ, Rudensky AY, et al. Expansion and function of Foxp3-expressing T regulatory cells during

tuberculosis. J Exp Med 2007;204:2159-69.
32. Logunova NN, Shepelkova GS, Apt AS. Regulatory T-Cells: Mechanisms of Immune Response Inhibtion and Involvement in the Control of Tuberculosis Infection. J Autoimmune Disord 2017;3:51.
33. Larson RP, Shafiani S, Urdahl KB. Foxp3(+) regulatory T cells in tuberculosis. Adv Exp Med Biol 2013;783:165-80.
34. Romero-Adrián T, Leal- Montiel J. Helicobacter pylori infection: Regulatory T cells and participation in the Regulatory T cell frequency and modulation of IFN-gamma and IL-17 in active and latent tuberculosis. Tuberculosis. immune response. Jundishapur J Microbiol 2013;6:e5183.
35. Marín ND, Paris SC, Vélez VM, Rojas CA, Rojas M, García LF. Regulatory T cell frequency and modulation of IFN gamma and IL17 in active and latent tuberculosis. Tuberculosis 2010;90:252-61.
36. De Almeida AS, Fiske CT, Sterling TR, Kalams SA. Increased frequency of regulatory T cells and T lymphocyte activation in persons with previously treated extrapulmonary tuberculosis. Clin Vaccine Immunol 2012;19:45-52.
37. Rahman S, Gudetta B, Fink J, Granath A, Ashenafi S, Aseffa A, et al. Compartmentalization of immune responses in human tuberculosis: few CD8+ effector T cells but elevated levels of FoxP3+ regulatory T cells in the granulomatous lesions. Am J Pathol 2009;174:2211-24.
38. Russell DG. Who puts the tubercle in tuberculosis? Nat Rev Microbiol 2007;5:39-47.
39. Korb VC, Chuturgoon AA, Moodley D. Mycobacterium tuberculosis: Manipulator of Protective Immunity. Int J Mol Sci 2016;17:131.
40. Cumming BM, Rahman MA, Lamprecht DA, Rohde KH, Saini V, Adamson JH, et al. Mycobacterium tuberculosis arrests host cycle at the G1/S transition to establish long term infection. PLoS Pathog 2017;13:e1006389.
41. Ising M, Holsboer F. Genetics of stress response and stress-related disorders. Dialogues Clin Neurosci 2006;8:433-44.
42. Ferguson LR, Shelling AN, Browning BL, Huebner C, Petermann I Genes, diet and inflammatory bowel disease. Mutat Res 2007;622:70-83.
43. Abel L, El-Baghdadi J, Bousfiha AA, Casanova J-L, Schurr E. Human genetics of tuberculosis: a long and winding road. Philos Trans R Soc Lond B Biol Sci 2014;369:20130428.
44. Schurr E. The contribution of host genetics to tuberculosis pathogenesis. Kekkaku J 2011;86:17-28.
45. Jepson A, Fowler A, Banya W, Singh M, Bennett S, Whittle H, Hill A. Genetic regulation of acquired immune responses to antigens of Mycobacterium tuberculosis: a study of twins in West Africa. Infect Immun 2001;69:3989-94.
46. Newport MJ, Goetghebuer T, Weiss HA, Whittle H, Siegrist C, Marchant A. Genetic regulation of immune responses to vaccines in early life. Genes Immun 2004;5:122-9.
47. Kimman T, Janssen R, Hoebee B. Future prospects in respiratory syncytial virus genetics. Future Virol 2006;1:483-92.
48. McShane H. Susceptibility to tuberculosis – the importance of the pathogen as well as the host. Clin Exp Immunol 2003;133:20-1.
49. Al-Muhsen S, Casanova J. The genetic heterogeneity of Mendelian susceptibility to mycobacterial diseases. J Allergy Clin Immun 2008;122:1043-51.
50. Lombard Z, Dalton D, Venter P, Williams R, Bornman L. Association of HLA-DR, -DQ, and vitamin D receptor alleles and haplotypes with tuberculosis in the Venda of South Africa. Hum Immunol 2006;67:643-54.
51. Wamala D, Buteme HK, Kirimunda S, Kallenius G, Joloba M. Association between human leukocyte antigen class II and pulmonary tuberculosis due to mycobacterium tuberculosis in Uganda. BMC Infect Dis 2016;16:23.
52. Fernández-Mestre M, Villasmil Á, Takiff H, Fuentes Alcalá Z. NRAMP1 and VDR Gene Polymorphisms in Susceptibility to Tuberculosis in Venezuelan Population. Dis Markers 2015;2015:860628.
53. Vejbaesya S, Chierakul N, Luangtrakool K, Srinak D, Stephens H. Associations of HLA class II alleles with pulmonary tuberculosis in Thais. Eur J Immunogenet 2002;29:431-4.
54. Qu H-Q, Fisher-Hoch SP, McCormick JB. Knowledge Gaining by Human Genetic Studies on Tuberculosis Susceptibility. J Hum Genet 2011;56:177-82.
55. Lindestam Arlehamn CS, McKinney DM, Carpenter C, Paul S, Rozot V, Makgotlho E, et al. A Quantitative Analysis of Complexity of Human Pathogen-Specific CD4 T Cell Responses in Healthy M. Tuberculosis Infected South Africans. Salgame P, ed. PLoS Pathogens 2016;12:e1005760.
56. Zhou F, Xu X, Wu S, Cui X, Fan L, Pan W. Influence of HLA-DRB1 Alleles on the Variations of Antibody Response to Tuberculosis Serodiagnostic Antigens in Active Tuberculosis Patients. PLoS ONE One 2016;11:e0165291.
57. Wyllie S, Seu P, Goss JA. The natural resistance associated macrophage protein 1 Slc11a1 (formerly Nramp1) and iron metabolism in macrophages. Microbes Infect 2002;4:351-9.
58. Huang L, Liu C, Liao G, Yang X, Tang X, Chen J. Vitamin D Receptor Gene FokI Polymorphism Contributes to Increasing the Risk of Tuberculosis: An Update Meta-

Analysis. Medicine (Baltimore) 2015;94:e2256.
59. Hoal E, Lewis L, Jamieson S, Tanzer F, Rossouw M, Victor T, et al. SLC11A1 (NRAMP1) but not SLC11A2 (NRAMP2) polymorphisms are associated with susceptibility to tuberculosis in a high-incidence community in South Africa. Int J Tuberc Lung D 2004;8:1464-71.
60. Li H, Zhang T, Zhou Y, Huang Q, Huang J. SLC11A1 (formerly NRAMP1) gene polymorphisms and tuberculosis susceptibility: a meta-analysis. Int J Tuberc Lung D 2006;10:3-12.
61. Vidyarani M, Selvaraj P, Prabhu AS, Jawahar M, Adhilakshmi A, Narayanan P. Interferon gamma (IFNgamma) & interleukin-4 (IL-4) gene variants & cytokine levels in pulmonary tuberculosis. Indian J Med Res 2006;124:403-10.
62. Wei Z, Wenhao S, Yuanyuan M, Yang L, Daming Z, Jiangchun X, et al. A single nucleotide polymorphism in the interferon-γ gene (IFNG +874 T/A) is associated with susceptibility to tuberculosis. Oncotarget 2017;8:50415-29.
63. Marlo Moller, Erika de Wit, Eileen G. Hoal. Past, present and future directions in human genetic susceptibility to tuberculosis. FEMS Immunol Med Microbiol 2010;58:3-26.
64. Lopez-Maderuelo D, Arnalich F, Serantes R, Gonzalez A, Codoceo R, Madero R, et al. Interferon-gamma and interleukin-10 gene polymorphisms in pulmonary tuberculosis. Am J Resp Crit Care 2003;167:970-5.
65. Tso H, Ip W, Chong W, Tam C, Chiang A, Lau Y. Association of interferon gamma and interleukin 10 genes with tuberculosis in Hong Kong Chinese. Genes Immun 2005;6:358-63.
66. Rossouw M, Nel H, Cooke G, van Helden P, Hoal E. Association between tuberculosis and a polymorphic NF kappa B binding site in the interferon gamma gene. Lancet 2003;361:1871-2.
67. Hobbs M, Udhayakumar V, Levesque M, Booth J, Roberts JM, Tkachuk AN, et al. A new NOS2 promoter polymorphism associated with increased nitric oxide production and protection from severe malaria in Tanzanian and Kenyan children. Lancet 2002;360:1468-75.
68. Jamaati H, Mortaz E, Pajouhi Z, Folkerts G, Movassaghi M, Moloudizargari M, Garssen J, et al. Front Microbiol 2017;8:2008.
69. Chan E, Chan J, Schluger N. What is the role of nitric oxide in murine and human host defense against tuberculosis? Current knowledge. Am J Resp Cell Mol 2001;25:606-12.
70. Pahari S, Kaur G, Negi S, Aqdas M, Das DK, Bashir H, et al. Reinforcing the Functionality of Mononuclear Phagocyte System to Control Tuberculosis. Front Immunol 2018;9:193.
71. Gomez L, Anaya J, Vilchez J, Cadena J, Hinojosa R, Velez L, et al. A polymorphism in the inducible nitric oxide synthase gene is associated with tuberculosis. Tuberculosis 2007;87:288-94.
72. Hasan Z, Zaidi I, Jamil B, Khan M, Kanji A, Hussain R. Elevated ex vivo monocyte chemotactic protein-1 (CCL2) in pulmonary as compared with extra-pulmonary tuberculosis. BMC Immunol 2005;6:14.
73. Mourik BC, Lubberts E, de Steenwinkel JEM, Ottenhoff THM, Leenen PJM. Interactions between Type 1 Interferons and the Th17 Response in Tuberculosis: Lessons Learned from Autoimmune Diseases. Front Immunol 2017;8:294.
74. Chang JT, Wherry EJ, Goldrath AW. Molecular regulation of effector and memory T cell differentiation. Nat Immunol 2014;15:1104-15.
75. Tabara Y, Kohara K, Yamamoto Y, Igase M, Nakura J, Kondo I, Miki T. Polymorphism of the monocyte chemoattractant protein (MCP-1) gene is associated with the plasma level of MCP-1 but not with carotid intima-media thickness. Hypertens Res 2003;26:677-83.
76. Jabot-Hanin F, Cobat A, Feinberg J, Orlova M, Niay J, Deswarte C, et al. An eQTL variant of ZXDC is associated with IFN-γ production following Mycobacterium tuberculosis antigen-specific stimulation. Sci Rep 2017;7:12800.
77. Jamieson S, Miller E, Black G, Peacock CS, Cordell HJ, Howson JM, et al. Evidence for a cluster of genes on chromosome 17q11-q21 controlling susceptibility to tuberculosis and leprosy in Brazilians. Genes Immun 2004;5:46-57.
78. Moller M, Nebel A, Valentonyte R, van Helden PD, Schreiber S, Hoal EG. Investigation of chromosome 17 candidate genes in susceptibility to TB in a South African population. Tuberculosis 2009;89:189-94.
79. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol 2004;4:499-511.
80. Quesniaux V, Fremond C, Jacobs M, Parida S, Nicolle D, Yeremeev V, et al. Toll-like receptor pathways in the immune responses to mycobacteria. Microbes Infect 2004;6:946-59.
81. Ferwerda G, Girardin S, Kullberg B Le Bourhis L, de Jong DJ, Langenberg DM, et al. NOD2 and tolllike receptors are nonredundant recognition systems of Mycobacterium tuberculosis. PLoS Pathog 2005;1:279-85.
82. Ma X, Liu Y, Gowen BB, Graviss EA, Clark AG, Musser JM. Full-exon resequencing reveals toll-like receptor variants contribute to human susceptibility to tuberculosis disease. PLoS One 2007;2:e1318.

83. Ogus A, Yoldas B, Ozdemir T, Uguz A, Olcen S, Keser I, et al. The Arg753GLn polymorphism of the human toll-like receptor 2 gene in tuberculosis disease. Eur Respir J 2004;23:219-23.
84. Holmskov U, Thiel S, Jensenius JC. Collections and ficolins: humoral lectins of the innate immune defense. Annu Rev Immunol 2003;21:547-78.
85. Turner M, Johnson M, Booth C, Klein N, Rolland J, Davies J. Assays for human mannose-binding lectin. J Immunol Methods 2003;276:147-9.
86. Yang D, Kong Y. The bacterial and host factors associated with extrapulmonary dissemination of Mycobacterium tuberculosis. Front Biol 2015;10:252-61.
87. Soborg C, Madsen H, Andersen A, Lillebaek T, Kok-Jensen A, Garred P. Mannose-binding lectin polymorphisms in clinical tuberculosis. J Infect Dis 2003;188:777-82.
88. Cosar H, Ozkinay F, Onay H, Bayram N, Bakiler AR, Anil M, et al. Low levels of mannose-binding lectin confers protection against tuberculosis in Turkish children. Eur J Clin Microbiol 2008;27:1165-9.
89. Ji X, Gewurz H, Spear GT. Mannose binding lectin (MBL) and HIV. Mol Immunol 2005;42:145-52.
90. Barreiro LB, Neyrolles O, Babb CL, Tailleux L, Quach H, McElreavey K, et al. Promoter variation in the DC-SIGN encoding gene CD209 is associated with tuberculosis. PLoS Med 2006;3:e20.
91. Klug-Micu GM, Stenger S, Sommer A, Liu PT, Krutzik SR, Modlin RL, et al. CD40 ligand and interferon-γ induce an antimicrobial response against Mycobacterium tuberculosis in human monocytes. Immunology 2013;139:121-8.
92. Areeshi MY, Mandal RK, Dar SA, Jawed A, Wahid M, Lohani M, et al. IL-10 -1082 A>G (rs1800896) polymorphism confers susceptibility to pulmonary tuberculosis in Caucasians but not in Asians and Africans: a meta-analysis. Biosci Rep 2017;37:BSR20170240.
93. Sudfeld CR, Mugusi F, Aboud S, Nagu TJ, Wang M, Fawzi WW. Efficacy of vitamin D3 supplementation in reducing incidence of pulmonary tuberculosis and mortality among HIV-infected Tanzanian adults initiating antiretroviral therapy: study protocol for a randomized controlled trial. Trials 2017;18:66.
94. Selvaraj P, Narayanan P, Reetha A. Association of vitamin D receptor genotypes with the susceptibility to pulmonary tuberculosis in female patients & resistance in female contacts. Indian J Med Res 2000;111:172-9.
95. Wilkinson R, Llewelyn M, Toossi Z, Patel P, Pasvol G, Lalvani A, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case control study. Lancet 2000;355:618-21.
96. Lee SW, Chuang TY, Huang HH, Liu CW, Kao YH, Wu LS. VDR and VDBP genes polymorphisms associated with susceptibility to tuberculosis in a Han Taiwanese population. J Microbiol Immunol Infect 2016;49:783-7.
97. Babb C, van der Merwe L, Beyers N, Pheiffer C, Walzl G, Duncan K, et al. Vitamin D receptor gene polymorphisms and sputum conversion time in pulmonary tuberculosis patients. Tuberculosis 2007;87:295-302.
98. Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. J Infect Dis 2015;211:S21-8.
99. Adekambi T, Ibegbu CC, Cagle S, Kalokhe AS, Wang YF, Hu Y, et al. Biomarkers on patient T cells diagnose active tuberculosis and monitor treatment response. J Clin Invest 2015;125:1827-38.
100. Portevin D, Moukambi F, Clowes P, Bauer A, Chachage M, Ntinginya NE, et al. Assessment of the novel T-cell activation marker-tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study. Lancet Infect Dis 2014;14:931-8.
101. Rozot V, Patrizia A, Vigano S, Mazza-Stalder J, Idrizi E, Day CL, et al. Combined use of Mycobacterium tuberculosis-specific CD4 and CD8 T-cell responses is a powerful diagnostic tool of active tuberculosis. Clin Infect Dis 2015;60:432-7.
102. Rozot V, Vigano S, Mazza-Stalder J, Idrizi E, Day CL, Perreau M, et al. Mycobacterium tuberculosis-specific CD8+ T cells are functionally and phenotypically different between latent infection and active disease. Eur J Immunol 2013;43:1568-77.
103. Nikitina IY, Kondratuk NA, Kosmiadi GA, Amansahedov RB, Vasilyeva IA, Ganusov et al. Mtb-Specific CD27low CD4 T cells as markers of lung tissue destruction during pulmonary tuberculosis in humans. PLoS One 2012;7:e43733.
104. Sutherland JS, Loxton AG, Haks MC, Kassa D, Ambrose L, Lee JS, et al. Differential gene expression of activating Fcγ receptor classifies active tuberculosis regardless of human immunodeficiency virus status or ethnicity. Clin Microbiol Infect 2014;20:O230-8.
105. Luo J, Zhang M, Yan B, Zhang K, Chen M, Deng S. Imbalance of Th17 and Treg in peripheral blood mononuclear cells of active tuberculosis patients. Braz J Infect Dis 2017;21:155-61.
106. Guedan S, Chen X, Madar A, Carpenito C, McGettigan SE, Frigault MJ et al. ICOS-based chimeric antigen receptors program bipolar TH17/TH1 cells. Blood 2014;124:1070-80.
107. Cosmi L, De Palma R, Santarlasci V, Maggi L, Capone M, Frosali F, et al. Human interleukin 17–producing cells

originate from a CD161+CD4+ T cell precursor. J Exp Med 2008;205:1903-16.

108. Grimaldi D, Le Bourhis L, Sauneuf B, Dechartres A, Rousseau C, Ouaaz F, et al. Specific MAIT cell behaviour among innate-like T lymphocytes in critically ill patients with severe infections. Intensive Care Med 2014;40:192-201.
109. Sharma PK, Wong EB, Napier RJ, Bishai WR, Ndung'u T, Kasprowicz V, et al. High expression of CD26 accurately identifies human bacteria-reactive MR1-restricted MAIT cells. Immunology 2015;145:443-53.
110. Coulter F, Parrish A, Manning D, Kampmann B, Mendy J, Garand M, et al. IL-17 Production from T Helper 17, Mucosal-Associated Invariant T, and γδ Cells in Tuberculosis Infection and Disease. Front Immunol 2017;11:1252.