Early clearance versus control: what is the meaning of a negative tuberculin skin test or interferon-gamma release assay following exposure to *Mycobacterium tuberculosis*?

Erin W. Meermeier\(^1\), David M. Lewinsohn\(^1,2\)

\(^1\)Pulmonary and Critical Care Medicine, Department of Medicine, Oregon Health and Science University, Portland, USA
\(^2\)Department of Medicine, VA Portland Health Care System, Portland, OR, USA

Abstract

The elimination of tuberculosis (TB) cannot reasonably be achieved by treatment of individual cases and will require an improved vaccine or immunotherapy. A challenge in developing an improved TB vaccine has been the lack of understanding what is needed to generate sterilizing immunity against *Mycobacterium tuberculosis* (Mtb) infection. Several epidemiological observations support the hypothesis that humans can eradicate Mtb following exposure. This has been termed early clearance and is defined as elimination of Mtb infection prior to the development of an adaptive immune response, as measured by a tuberculin skin test or interferon-gamma release assay. Here, we examine research into the likelihood of and possible mechanisms responsible for early clearance in household contacts of patients with active TB. We explore both innate and adaptive immune responses in the lung. Enhanced understanding of these mechanisms could be harnessed for the development of a preventative vaccine or immunotherapy.

Keywords

*Mycobacterium tuberculosis*, preventative vaccine, infection, household contact studies

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1. Françoise Mascart, Université Libre de Bruxelles, Brussels, Belgium
2. Catherine Stein, Case Western Reserve University School of Medicine, Wolstein Research Building, Cleveland, USA

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Introduction

Tuberculosis (TB) is a leading cause of infectious disease mortality worldwide, accounting for approximately 6.3 million new cases and 1.4 million deaths in 2016 (World Health Organization [WHO] TB Report 2017). The recent emergence of strains of *Mycobacterium tuberculosis* (Mtb) resistant to nearly all effective drug therapy highlights the need for alternative strategies to TB control. The Bacille Calmette–Guérin (BCG) vaccine has been widely used but is controversial, as its efficacy for the prevention of adult TB has been variable. Moreover, despite the widespread use of the BCG vaccine worldwide, the incidence of TB has not dramatically decreased. The elimination of TB cannot reasonably be achieved by treatment of individual cases and will require an improved vaccine or early detection of those likely to progress. The main challenge in developing an improved TB vaccine has been the lack of understanding correlates of protective immunity. What is needed to generate sterilizing immunity against Mtb infection, unlike in many other preventable infectious diseases, is still unknown.

Mtb is transmitted via the aerosol delivery of small particulates into the lung. Here, a dynamic interplay between host immune mechanisms and the virulent bacterium begins with the innate immune system. Innate immunity provides functional and immediate defenses against microbial infection through shared germline-encoded processes and receptors. In addition to the direct recognition and control of microbial infection, innate immunity plays a central role in the initiation and maintenance of subsequent adaptive immune responses. In the lung, Mtb can interact with and infect different cell types, including macrophages, and can establish stable intracellular infection. When infection overcomes initial physical and immunological defenses, exposure to pathogen-derived antigens leads to an adaptive immune response over the ensuing two to six weeks. This response relies upon clonal expansion of antigen-specific lymphocytes and forms the basis for immunological memory. Tuberculin skin tests (TSTs) and interferon-gamma release assays (IGRAs) measure immune sensitization to Mtb and can reflect whether infection has occurred. Individuals who test positively with a TST or IGRA but have no evidence of TB are considered to have latent tuberculosis infection (LTBI). Among LTBI individuals, the estimated lifetime risk of developing TB is roughly 10% (WHO Global TB Report 2016). Neither the TST nor the IGRA can serve as a reflection of bacterial burden. Nonetheless, in the setting of a household exposure, both tests have excellent negative predictive values in that they predict those who are unlikely to get TB.

Upon exposure to Mtb, a number of disparate outcomes can occur. These outcomes include no infection, early clearance of infection, LTBI, and TB (Figure 1). Although about one-quarter of the global population is thought to be infected with Mtb, these epidemiological observations indicate that humans have evolved mechanisms to control or eradicate infection with Mtb. First, some individuals repeatedly exposed to Mtb never demonstrate evidence of immune sensitization by TST or IGRA. These individuals may have been able to eradicate Mtb with an effective innate immune response before an adaptive immune response develops. This phenomenon is termed early clearance. Second, a subset of individuals with a positive TST or IGRA have been observed to revert to a negative result over time. Reversion of these tests may indicate a decrease in bacterial load or clearance of infection and is suggestive of control of Mtb infection. Third, of the individuals considered to have LTBI, exposure to pathogen-derived antigens leads to an adaptive immune response over the ensuing two to six weeks. This response relies upon clonal expansion of antigen-specific lymphocytes and forms the basis for immunological memory. Tuberculin skin tests (TSTs) and interferon-gamma release assays (IGRAs) measure immune sensitization to Mtb and can reflect whether infection has occurred. Individuals who test positively with a TST or IGRA but have no evidence of TB are considered to have latent tuberculosis infection (LTBI). Among LTBI individuals, the estimated lifetime risk of developing TB is roughly 10% (WHO Global TB Report 2016). Neither the TST nor the IGRA can serve as a reflection of bacterial burden. Nonetheless, in the setting of a household exposure, both tests have excellent negative predictive values in that they predict those who are unlikely to get TB.

![Figure 1. Outcomes of exposure to *Mycobacterium tuberculosis* (Mtb).](image_url)

Mtb exposure can lead to infection, early clearance, latent tuberculosis infection, or, ultimately, tuberculosis. Early clearance occurs before the development of an adaptive immune response detected by a tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Understanding of the underlying mechanisms dictating the outcomes of exposure to Mtb could greatly facilitate the definition of correlates of protective immunity to Mtb infection and generate targets of a preventative vaccine. Possible mechanisms responsible for early clearance in household contacts of active tuberculosis patients that are explored in this review are listed on the right (orange).
most contain infection without developing TB, indicating the development of protective immunity. Although those with LTBI are at risk of reactivation, studies of nursing and medical students in the early twentieth century suggest that a history of infection with Mtb correlates with less risk of TB over a lifetime in a subset of individuals. This suggests that prior exposure to Mtb could be protective\(^6\). Evidence to support these three cases of resistance to Mtb has been highlighted in two reviews published in 2014\(^{10,11}\). Nevertheless, early clearance of Mtb infection has been the focus of intensified research over the past three years. Understanding of these events could greatly facilitate the definition of correlates of protective immunity to Mtb infection.

In this commentary review, we present and summarize recent research advances in understanding the epidemiology of early clearance of Mtb infection. We include studies of loci of resistance, mechanisms of early clearance, and natural transmission model systems and instigate discussion of the relevance of these advances to vaccines to control infection by Mtb.

**Evidence for early clearance**

A difficulty in studying early clearance of Mtb infection has been discerning it from non-exposure, as lack of converting a TST or IGRA could reflect either situation. In the absence of a gold standard for diagnosing Mtb infection, it is possible that either test could miss instances of infection. However, given the excellent negative predictive value of both tests, we will consider either test could miss instances of infection. Nevertheless, early clearance of Mtb infection has been the focus of intensified research over the past three years. Understanding of these events could greatly facilitate the definition of correlates of protective immunity to Mtb infection. For example, a Uganda–Case Western Reserve University research collaboration has been conducting a long-standing study of HCs since 1995. Recently compiled data from this study were used to define risk factors of Mtb infection as measured by TST positivity in over 1,300 individuals. Among adult HCs, there were no significant differences in a multifactorial risk score between individuals who were persistently TST-negative and those who had a positive TST or converted to a positive TST over two years\(^{12}\). This result was further supported by a culminating analysis of over 2,500 HCs from the same cohort\(^3\). Here, persistently TST-negative adults did not differ in epidemiologic risk score from other clinical groups. These data suggest that there is still evidence for early clearance even when the degree of exposure is controlled for.

A number of different studies have tried to establish the prevalence of early clearance. Here, the prevalence of early clearance of infection can be defined by a persistent negative TST or IGRA in the setting of Mtb exposure. In humans, our best examples of early clearance come from longitudinal (two-plus years) analyses of HCs of TB patients, or those residing in high TB-burden areas, where immune sensitization is carefully monitored. Table 1 and Table 2 summarize longitudinal studies of HCs categorized as persistently TST-negative (Table 1) or persistently TST- or IGRA-negative or both (Table 2). As illustrated in Table 1, studies with at least two years of longitudinal observation of HC conversion of TST demonstrated a frequency of early clearance ranging from 3.4\(^{13}\) to 26.8\(^{14}\), both in Uganda\(^b\). Whereas the TB Network study that followed HC conversion of IGRA demonstrated that about 58\% of exposed HCs lacked evidence of immune sensitization, other studies had a less rigorous definition, as they varied by time of follow-up with individual as well as the likelihood of exposure to TB\(^{15-30}\). Presumably, in some of these studies, higher rates

### Table 1. Studies that have determined persistent tuberculin skin test negativity in household contacts.

| Location          | Duration of observation | Household contacts | Percentage TST-negative | Reference |
|-------------------|-------------------------|--------------------|-------------------------|-----------|
| Uganda\(^a\)      | 2 years                 | 97                 | 26.8                    | 15        |
| Uganda\(^a\)      | 2 years                 | 2,585              | 9.9                     | 21        |
| Tanzania and Uganda | Up to 8 years          | 469                | 48                      | 22        |
| Venezuela\(^a\)   | 3 years                 | 102\(^d\)          | 18.6                    | 23        |
| Uganda\(^a\)      | 2 years                 | 601                | 14.5                    | 24        |
| The Gambia\(^a\)  | 6 months                | 64                 | 60                      | 20        |
| Uganda\(^a\)      | 2 years                 | 1,318              | 11.7                    | 12        |
| Uganda\(^a\)      | 1–2 years               | 529                | 3.4                     | 25        |
| South Africa      | None                    | 350                | 40                      | 14        |
| Pakistan          | 2 years                 | 93                 | 25                      | 26        |
| Ghana             | None                    | 2,346              | 5.5                     | 19        |
| Uganda\(^a\)      | 2 years                 | 803                | 10.5                    | 27        |

\(^a\)Subjects were from the same cohort; \(^b\)not a high tuberculosis burden area; \(^c\)all patients were HIV-positive and only 46% of persons enrolled were household contacts; \(^d\)tuberculosis hospital workers, not household contacts. TST, tuberculin skin test.
Mechanisms of early clearance of *Mycobacterium tuberculosis* infection

Initial recognition of aerosolized Mtb occurs in the lung, which leads to the production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides (reviewed in 28,29). What determines the outcome of exposure to Mtb? Is infection determined by the virulence of the microbe or more dependent upon host response? Is the immediate response in the respiratory tract important to host protection? Is infection determined by the ability of Mtb to establish a niche in a specific inflammatory microenvironment? Or does the quality, quantity, or organization of lung-resident lymphocytes influence early killing of Mtb and ultimate protection of the host?

I. Early recognition of *Mycobacterium tuberculosis*

The airway is a complex immune organ and likely critical in determining the outcome of Mtb exposure. It exhibits anatomic and functional heterogeneity and contains a diverse array of mechanisms to prevent pulmonary infection, including mucociliary clearance, secreted antibodies, and antimicrobial proteins such as defensins28. Although most research has focused on the alveolus as the initial site of infection, Mtb has ample opportunity to interact with the entire respiratory tract, like other aerosolized particulates. However, how these interactions result in clinically relevant outcomes such as infection and progression to disease is poorly understood. Reuschl et al. used polarized human lung epithelial cells in conjunction with myeloid cells to model these early interactions. Following Mtb infection, they mapped global transcriptomic changes in host cells. Interestingly, they found that myeloid cells could license epithelial cells, through interleukin-1 beta (IL-1β) and type I interferon, resulting in enhanced mycobacterial control29. Additionally, following Mtb infection in the mouse, cathelicidins and related antimicrobial proteins produced by lung macrophages and epithelial cells were required for early clearance of infection1. Mounting evidence suggests a role of humoral immunity, including antibodies, and antibody-responsive innate immune cells bearing Fc-receptors, in protective immunity to Mtb32–34. While studying patients already infected with Mtb, Lu et al. explored 70 different antibody features of total serum IgG from patients with LTBI compared with active TB. The authors’ data suggested an innate antibody Fc effector profile which led to the restriction of bacterial survival within macrophages35. When evaluating HCs of patients with active TB, Chin et al. observed a different IgA antibody V-gene/D-segment repertoire in those without LTBI compared with those with LTBI, suggesting that a specific type of secretory IgA may promote mucosal protection from Mtb infection36. A recently published genome-wide association study of persistently TST-negative HIV-positive HCs investigated mechanisms of resistance to infection37. Here, HIV-positive contacts who resisted Mtb infection were postulated to have robust innate immunity. Sobota et al. found a significant association between TST negativity with a single-nucleotide polymorphism (SNP) at 5q31.1, which is located between *SLC25A48*, a mitochondrial amino acid transporter, and *IL-9*, a cytokine38. IL-9 has been implicated in bronchial hyperreactivity and as a growth factor for mast cells and T cells22. In an effort to search for biomarkers of stages of Mtb infection, Bark et al. evaluated HCs prospectively for differences in serum proteins over two years using mass spectrometry. They compared changes in host proteins in those who were persistently TST- and IGRA-negative, had LTBI, or had TB39. Tissue integrity proteins, such as keratins, hornerin, lumican, and a component of the extracellular matrix, were more highly expressed in the serum of HCs who did not convert their TST and IGRA. It is interesting to speculate whether these proteins contribute to an essential early barrier against infection. Taken together, these data suggest a distinct role for the respiratory tract as the first line of defense against Mtb infection.

II. Cell-intrinsic mechanisms of host resistance

Mtb virulence is a critical determinant of disease outcome following exposure. Although virulence must be broadly defined, one aspect is certainly the ability of the microbe to circumvent host immunity, such that the outcome reflects this complex interaction. It has been observed that the acquisition of adaptive immunity following infection with Mtb is delayed compared with other infections37,38. As a result, it has been postulated that Mtb has developed immune-evasive mechanisms to orchestrate this delay, allowing unrestricted replication in the lung. In fact, while using a low-dose aerosol model of TB in non-human primates, Gideon et al. asked whether there are differences in the immune response upon initial infection that determine the severity of the
outcome. Through longitudinal blood transcriptome analysis, these data suggested that a highly orchestrated innate and adaptive immune response was crucial for containment of the bacilli.

To determine whether HCs who resist infection or have LTBI differ in their ability to produce innate cytokines in response to Mycobacterium tuberculosis (Mtb) infection, Mahan et al. employed a whole blood enzyme-linked immunosorbent assay. Here, the responses to a panel of innate receptor ligands indicated no differences between HCs with or without LTBI. Although these data imply similar innate immune capabilities between those who remain TST-negative and those with LTBI, the authors state the need for more comprehensive study of innate protective mechanisms. Correspondingly, a subsequent study in HCs from the same district indicated that initial recognition of Mtb by distinct innate receptors contributes to controlling infection. Hall et al. performed comparative candidate immune gene SNP analysis in HCs with or without LTBI. They found SNPs in NOD1, NOD2, SLC6A3, STAT1, IL12RB1, IL12RB2, and TLR4 that associated with a persistently negative TST. As these are intracellular and extracellular sensors of bacteria, this suggests the need for recognition of infection and activation of the host cell in memory. Interestingly, NOD2 signaling is increased post-BCG vaccination for up to one year through a phenomenon called trained immunity. Trained immunity is defined as resistance to re-infection and is thought to reflect persistent changes in innate pathways that can lead to memory. Further information from Manzanillo et al. supports intracellular sensing; phagosome acidification of Mtb can be triggered through another cytosolic surveillance pathway recognizing microbial cyclic dinucleotides and DNA. These data indicate that intracellular sensing of Mtb in the host cell is a crucial trigger to controlling the early infection.

A common feature of innate sensing of extracellular and intracellular Mtb is host cell activation, resulting in microbial killing. Host cells can directly kill Mtb by the production of antimicrobial proteins, reactive oxygen species, and acidification of the phagosome. Acidification leads to autophagy, which in turn may help prevent or limit infection. Horne et al. found that a human SNP in ULK1 was associated with infection. CRISPR/Cas9 gene editing to delete ULK1 revealed that its deficiency in macrophages resulted in augmented Mtb growth, diminished tumor necrosis factor-alpha (TNF-α) production, and diminished autophagy. Other genes associated with the macrophage phagosome, such as SLC11A1 or natural resistance-associated macrophage protein 1 (NRAMP1), have been linked to the development of TB previously. Although its full function remains to be elucidated, three studies have identified phagosome-associated NRAMP1 expression as a protein associated with resistance to infection with Mtb. A seminal study of HCs in Uganda used a genome-wide linkage analysis to reveal three regions associated with early clearance. Whereas the two most significant regions did not contain characterized genes, a third contained NRAMP1. Also, an NRAMP1 polymorphism in the 3′ untranslated region (UTR) was more common in Venezuelan hospital workers who were persistently TST-negative than those with LTBI. Additionally, the transcriptome of host cell monocytes derived from persistently TST-negative HCs compared with those with LTBI has been explicitly interrogated by Seshadri et al.

Transcripts associated with histone deacetylase (HDAC) inhibition were enriched among persistently TST-negative HCs. Using chemical inhibition of HDACs in monocytes in vitro, the authors observed a role for HDACs in the early immune response to Mtb infection. As HDACs are associated with closed chromatin, this study would support a role for epigenetic programming of host cells in the control of Mtb infection.

Lastly, macrophages capable of non-inflammatory apoptosis and efferocytosis have inherently improved mycobacterial control by limiting intercellular spread. Recent work in animal models of natural transmission supports the hypothesis that augmented apoptosis can result in better control of Mtb infection. In this regard, cows that demonstrate resistance to Mycobacterium bovis infection have persistent TST negativity following herd exposure. To explore these mechanisms in cattle, Wu et al. generated an sp110-TALEN-mediated knock-in cow strain. The gene Ipr1/sp110 had been previously demonstrated to be associated with innate immunity to TB in mice. Sp110 is a nuclear body that permits apoptosis over inflammation. In the context of Mtb infection, in part through modification of the inflammasome. Subsequently, it is interesting that Mtb-infected macrophages from TST-negative cattle were recently shown to produce more NO. Therefore, NO, a molecule made in abundance in human lung epithelial cells, has additional functions that may contribute to preventing infection with Mtb. These studies advocate that non-inflammatory cell death and innate antimicrobial responses derived from genetics or trained epigenetics of the host cell can contribute to controlling Mtb infection.

III. Unconventional lymphocytes coordinate early lung inflammation to limit Mycobacterium tuberculosis infection

Longitudinal case control studies (Table 1 and Table 2) would indicate that infection by Mtb can be controlled without an adaptive T-cell response. In addition to macrophages, lymphocytes, especially T cells, could orchestrate this response to Mtb infection. In addition to antigen-specific HLA-I and HLA-II restricted cells that can be reflected in a TST and IGRA, a variety of cells are capable of recognizing the Mtb-infected cell that may not be reflected in these assays. First, it is possible that a TST or IGRA test fails to reflect lung-resident memory T cells that do not circulate systemically. Specifically, it has been argued that classically restricted tissue-resident memory T cells may recognize Mtb-infected cells and confer protection before the acquisition of a peripheral adaptive immune response. Second, unconventional T cells, including CD1-restricted cells, MR1-restricted mucosal-associated invariant T (MAIT) cells, HLA-E/Qa-1-restricted cells, and γδ T cells, can also recognize
Mtbc infection and are poised at mucosal sites such as the lung. Each of these cell populations can also kill infected host cells through cytotoxic granules and produce cytokines in the context of Mtbc. Mouse models of TB have been used to decipher whether these subsets have a protective role in the antimicrobial immune response. Using mice deficient in the antigen-presentation element, researchers have observed a role for MR1-restricted MAIT cells and Qa-1-restricted cells in the early response to Mtbc infection. In parallel experiments, group I CD1-restricted T cells specific to Mtbc-derived lipids conferred protection in human CD1-transgenic mice. Mouse models of TB do not suggest a non-redundant role for natural killer T cells or γδ T cells in a chronic TB setting, although they do show changes in frequency and phenotype in association with human Mtbc infection. Moreover, group-I CD1-, HLA-E-, and MR1-restricted T cells specific to Mtbc antigen have been detected in individuals with active or LTBI infection. Collectively, these studies indicate a strong possibility that lung-resident T-cell populations play a role in the early immune response to Mtbc in humans.

Lastly, natural transmission models of Mtbc infection in guinea pigs have provided us with an important example of sterilizing adaptive immunity. Guinea pigs demonstrate a range of susceptibility to Mtbc infection in natural transmission experiments. A unique set-up of these experiments includes the direct exposure of guinea pigs to air from patients. They reflect many features of human immunity such as variable progression to disease. Additionally, some guinea pigs displayed the early clearance phenotype in that they became infected and then reverted to a negative TST. Sterilizing immunity was supported by the observation that the animals did not have granulomas or culturable mycobacteria, and conversion was prevented by irradiating the air. Furthermore, administration of dexamethasone did not result in TB. As the prevalence of sterilizing immunity in humans is uncertain, future lessons from model systems may provide a paradigm of immune memory that may be crafted into future vaccine strategy or immune therapeutics.

The immune race to control Mycobacterium tuberculosis infection

Viewed in aggregate, the studies presented here illustrate immune mechanisms that may facilitate early clearance or the eradication of Mtbc before an adaptive immune response develops. In humans, our best indicators of early clearance come from longitudinal (two-plus years) analyses of HCs of TB patients or those residing in high TB burden areas, where exposure to Mtbc and immune sensitization are carefully monitored. It is important to recognize that much of our knowledge of the host-defense mechanisms comes from the study of those with chronic disease. However, studies focusing on the early acute phases of Mtbc infection have provided insights that support early and successful lung-resident immunity as key for preventing infection. As TB eradication will depend on preventing transmission, understanding immune correlates, such as improved macrophage function, mucosal antibodies, or enhanced recognition of the infected cell, will present new opportunities to prevent Mtbc infection.

Abbreviations

BCG, Bacille Calmette–Guérin; HC, household contact; HDAC, histone deacetylase; HLA, human leukocyte antigen; IGRA, interferon-gamma release assay; IL, interleukin; LTBI, latent tuberculosis infection; MAIT, mucosal-associated invariant T; Mtbc, Mycobacterium tuberculosis; NO, nitric oxide; NRAMP1, natural resistance-associated macrophage protein 1; SNP, single-nucleotide polymorphism; TB, tuberculosis; TST, tuberculin skin test; WHO, World Health Organization

Competing interests

The authors declare that they have no competing interests.

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macrophage responses to Mycobacterium bovis among naturally exposed uninfected and infected cattle. Immunol Cell Biol. 2017; 95(6): 436–42. PubMed Abstract | Publisher Full Text | F1000 Recommendation

51. Pan H, Yan BS, Rojas M, et al.: Il1 gene mediates innate immunity to tuberculosis. Nature. 2005; 434(7034): 767–72. PubMed Abstract | Publisher Full Text | F1000 Recommendation

52. Wu Y, Guo Z, Yao K, et al.: The Transcriptional Foundations of SpI10-mediated Macrophage (RAW264.7) Resistance to Mycobacterium tuberculosis H37Ra. Sci Rep. 2016; 6: 22041. PubMed Abstract | Publisher Full Text | F1000 Recommendation

53. Wu H, Wang Y, Zhang Y, et al.: TALE nickase-mediated SpI10 knockin endows cattle with increased resistance to tuberculosis. Proc Natl Acad Sci U S A. 2015; 112(13): E1530–9. PubMed Abstract | Publisher Full Text | F1000 Recommendation

54. Mishra BB, Lovewell RR, Olieve AJ, et al.: Nitric oxide prevents a pathogen-permissive granulocytic inflammation during tuberculosis. Nat Microbiol. 2017; 2: 17072. PubMed Abstract | Publisher Full Text | F1000 Recommendation

55. Garcia-Jacobs RE, Serrano CJ, Enciso Moreno JA, et al.: Analysis of Th1, Th17 and regulatory T cells in tuberculosis case contacts. Cell Immunol. 2014; 289(1–2): 167–73. PubMed Abstract | Publisher Full Text

56. Riaño F, Arroyo L, París S, et al.: T cell responses to DosR and Rpf proteins in actively and latently infected individuals from Colombia. Tuberculosis (Edinb). 2012; 92(2): 148–59. PubMed Abstract | Publisher Full Text

57. Hesseling AC, Mandalakas AM, Kirchner HL, et al.: Highly discordant T cell responses in individuals with recent exposure to household tuberculosis. Thorax. 2009; 64(10): 840–6. PubMed Abstract | Publisher Full Text

58. Leyton EM, Lin MY, Franken KL, et al.: Human T-Cell responses to 25 novel antigens encoded by genes of the dormancy regulon of Mycobacterium tuberculosis. Microbes Infect. 2006; 8(6): 2052–60. PubMed Abstract | Publisher Full Text

59. Godfrey DI, Uldrich AP, McCluskey J, et al.: The Transcriptional Foundations of Sp110-CD8+ T cell responses to DosR and Rpf proteins in humans. J Immunol. 2016; 197(1): 582–93. PubMed Abstract | Publisher Full Text

60. Masopust D, Picker LJ: Hidden memories: frontline memory T cells and early pathogen interception. J Immunol. 2012; 188(12): 5811–7. PubMed Abstract | Publisher Full Text | Free Full Text

61. Beverley PC, Sridhar S, Lalvani A, et al.: Harnessing local and systemic immunity for vaccines against tuberculosis. Mucosal Immunol. 2014; 7(1): 20–6. PubMed Abstract | Publisher Full Text

62. Horvath CN, Shaler CR, Jeyanathan M, et al.: Mechanisms of delayed anti-tuberculosis protection in the lung of parenteral BCG-vaccinated hosts: a critical role of airway luminal T cells. Mucosal Immunol. 2012; 5(4): 420–31. PubMed Abstract | Publisher Full Text

63. Jeyanathan M, Heriaziun A, Xing Z: Airway luminal T cells: a newcomer on the stage of TB vaccination strategies. Trends Immunol. 2010; 31(7): 247–52. PubMed Abstract | Publisher Full Text

64. Šakala IG, Kier-Nielsen L, Eickhoff CS, et al.: Functional Heterogeneity and Antimycobacterial Effects of Mouse Mucosal-Associated Invariant T Cells Specific for Riboflavin Metabolites. J Immunol. 2015; 195(2): 587–601. PubMed Abstract | Publisher Full Text | Free Full Text

65. Chua WJ, Truscott SM, Eickhoff CS, et al.: Polyclonal mucosa-associated invariant T cells have unique innate functions in bacterial infection. Infect Immun. 2012; 80(9): 3256–67. PubMed Abstract | Publisher Full Text | Free Full Text

66. Biao Y, Shang S, Siddiqui S, et al.: MHC Ib molecule Qa-1 presents Mycobacterium tuberculosis peptide antigens to CD8+ T cells and contributes to protection against infection. PLoS Pathog. 2017; 13(5): e1006384. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

67. Felio K, Nguyen H, Dascher CC, et al.: CD1-restricted adaptive immune responses to Mycobacteria in human group 1 CD1 transgenic mice. J Exp Med. 2009; 206(11): 2497–509. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

68. Zhao J, Siddiqui S, Shang S, et al.: Mycolic acid-specific T cells protect against Mycobacterium tuberculosis infection in a humanized transgenic mouse model. eLife. 2015; 4: pii: e08825. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

69. Arora P, Foster EL, Porcelli SA: CD1d and natural killer T cells in immunity to Mycobacterium tuberculosis. Adv Exp Med Biol. 2013; 783: 199–223. PubMed Abstract | Publisher Full Text

70. Chen ZW: Multifunctional immune responses of HMMP-specific V2V2i2 T cells in M. tuberculosis and other infections. Cell Mol Immunol. 2013; 10(1): 58–64. PubMed Abstract | Publisher Full Text | Free Full Text

71. Joosten SA, van Meijgaarden KE, van Weeren PC, et al.: Mycobacterium tuberculosis peptides presented by HLA-E molecules are targets for human CD8+ T cells with cytotoxic as well as regulatory activity. PLoS Pathog. 2010; 6(2): e1000782. PubMed Abstract | Publisher Full Text | Free Full Text

72. Lewinsohn DM, Briden AL, Reed SG, et al.: Mycobacterium tuberculosis-reactive CD8+ T lymphocytes: the relative contribution of classical versus nonclassical HLA restriction. J Immunol. 2000; 165(2): 925–30. PubMed Abstract | Publisher Full Text

73. Koosar AG, van Rhijn I, Cheng TY, et al.: CD8+ T-cell tetramers bind up T cell receptors to identify a mycobacterial glycolipid-reactive T cell repertoire in humans. J Exp Med. 2011; 208(9): 1741–7. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

74. Montanari-Gicote DJ, Millington KA, Wilcox CR, et al.: A mycolic acid-specific CD1-restricted T cell population contributes to acute and memory immune responses in human tuberculosis infection. J Clin Invest. 2011; 121(6): 2493–503. PubMed Abstract | Publisher Full Text | Free Full Text

75. Gold MC, Carr S, Smyk-Pearson S, et al.: Human mucosal associated invariant T cells detect bacterially infected cells. PLoS Biol. 2010; 8(6): e1000407. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

76. Riley RL, Mills CC, Nylä W, et al.: Aerial dissemination of pulmonary tuberculosis. A two-year study of contagion in a tuberculosis ward. 1959. Am J Epidemiol. 1995; 142(1): 3–14. PubMed Abstract | Publisher Full Text

77. Dharmadhikari AS, Basarabka RJ, Van Der Walt ML, et al.: Natural infection of guinea pigs exposed to patients with highly drug-resistant tuberculosis. Tuberculosis (Edinb). 2011; 91(4): 329–38. PubMed Abstract | Publisher Full Text | Free Full Text
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