AUCTORES
Globalize your Research

International Journal of BioMed Research
Mahendra K. Bhopale *

Open Access

Review Article

Aspects of Cytokine Response to HIV-1 and Tuberculosis Co-Infection

Mahendra K. Bhopale

Department of Microbiology, R.D. Gardi Medical College, Ujjain, MP 456001, India

***Corresponding author:** Mahendra K. Bhopale, Ph.D., D.Sc, Director (Research), R.D. Gardi Medical College, Ujjain, MP 456001, India

Received Date: August 03, 2021; **Accepted Date:** August 23, 2021; **Published Date:** November 19, 2021

Citation: Mahendra K. Bhopale (2021) Aspects of Cytokine Response to HIV-1 and Tuberculosis Co-Infection *International J. of Biomed Research*. 1(9); DOI: 10.31579/IJBR-2021/034

Abstract:

It has been known that HIV-1 infection alters the course of *Mycobacterium tuberculosis* infection and substantially increases the risk of active tuberculosis (TB). Various cytokines play different roles in HIV-1 and TB individually and in a co-infection stage of disease. IL-2 play CD4+ proliferation, IL-4 activate B cells, CD4 cell IL-6/IL-10 dysregulate and CD4+ T (Th17) cell subset lost during HIV-1 infection. IL-22 and IL-27-producing CD4 (+) T cells play immune reconstitution inflammatory syndrome (IRIS) following the commencement of antiretroviral therapy (ART). Higher values of IFN-γ, IL-2, IL-6 and IL-10 were observed in HIV-positive during anti-tuberculous treatment. Combination antiretroviral therapy in tuberculosis (TB) and HIV-1 infection is associated with an immune reconstitution inflammatory syndrome (TB-IRIS). Based on different roles of each cytokine in HIV-1 and TB individually and co-infection, changes occur in therapy is described in the present review.

Keywords: cytokine, HIV-1; tuberculosis; co-infection; immune mechanism

Abbreviations:

TB: Tuberculosis;

TB: Tuberculosis;

TPE: Tuberculous pleural effusion;

TB-IRIS: TB-associated immune reconstitution inflammatory syndrome IRIS: immune reconstitution inflammatory syndrome;

MTB: Mycobacterium tuberculosis;

HIV-1: human immunodeficiency virus type 1;

DC-SIGN: Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin;

ART: antiretroviral therapy;

HAART: Highly active antiretroviral therapy;

JAK/STAT: Janus kinase/signal transducers and activators of transcription;

PAMPs: pathogen-associated molecular patterns;

HLA-DR: Human Leukocyte Antigen–DR isotype;

AIDS: Acquired immunodeficiency syndrome;

NKT: Natural killer T cells;

PBMC: peripheral blood mononuclear cell;

LTB: Latent tuberculosis;

MDR-TB: Multidrug-resistant tuberculosis;

MDSC: Myeloid-derived suppressor cells;

EFV: Efavirenz;

RAL: Raltegravir;

7-oxoDHEA: 7-oxodehydroepiandrosterone;

NRTIs: Nucleoside reverse transcriptase inhibitors;

TLR: Toll-like receptor;

RNAi: RNA interference;

MYD88: Myeloid differentiation primary response 88;

IRAK1: Interleukin-1 receptor-associated kinase 1;

NRTIs: Nucleoside reverse transcriptase inhibitors;

NNRTIs: Non-nucleoside Reverse Transcriptase Inhibitors;

TRAF6: Tumor necrosis factor receptor-associated factor 6;

TREM-1: Triggering receptor expressed on myeloid cells 1;

MDR-TB: Multidrug-resistant tuberculosis

Introduction

The World Health Organization (WHO) estimated approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB) and active disease with human immunodeficiency virus type 1 (HIV-1) infection, mainly in Africa. HIV co-infection is known risk factor for progression of *M. tuberculosis* infection to active disease and increasing the risk of latent TB reactivation. HIV and tuberculosis (TB) co-infections have an immense health problem in diagnostic and therapeutic challenges [1-4]. In *M. tuberculosis* and HIV co-infection, both potentiate and accelerating one another in deterioration of immunological functions resulting in premature death of infected host, if untreated.

HIV infection is the depletion of $CD4^+$ T cells. The immunopathogenic features together systemic and chronic state of immune activation accelerated T cell contribute to the progression of HIV disease and the loss of immune balance between Th17 and regulatory T cells (Treg) during HIV disease. Cell-mediated immunity during *M. tuberculosis* infection is essential for control of activation of both $CD4^+$ and $CD8^+$ T cells [5-7]. T cells recruited to the infected lung are thought to control infection by producing IFN-γ in response to mycobacterial antigens presented by macrophages. It has been reported that DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans- infection of T cells [8]. An immune reconstitution inflammatory syndrome (IRIS) develops in *M. tuberculosis* and HIV co- infected patients undergo anti-TB treatment and antiretroviral therapy (ART) [9, 10]. TB patients present with an exacerbation of symptoms and radiological manifestations recognize predictors of IRIS in low $CD4^+$ T lymphocyte counts and high plasma viral load prior to initiation of ART. $CD4^+$ counts increase after highly active antiretroviral therapy (HAART) onset.

Though combination antiretroviral therapy (ART) has significantly improved the clinical outcome, they develop hyper inflammatory reactions. Antiretroviral treatment (ART) reduces the risk of developing active tuberculosis (TB) in HIV-1 co-infected patients. RNAseq analysis of whole blood-derived RNA from individuals with latent TB infection co-infected with HIV-1, a significant fall in RNA sequence abundance of the Hallmark IFN-α, IFN-γ, IL-6/JAK/STAT3 signaling to indicate reduced immune activation and inflammation. ART-induced decrease in immune activation combined with the improved antigen responsiveness, contributes to reduced susceptibility to tuberculosis in HIV-1/Mtb co-infected persons.

Based on different roles of cytokines in HIV-1, tuberculosis (TB) and co-infection during the disease and the therapy is described in the present review.

Cytokine roles in HIV, Tuberculosis and HIV-1 Tuberculosis co-infection

Interleukin-2 (IL-2) role. IL-2 cytokine is a glycoprotein that stimulates the growth of T cell lymphocytes. The major sources of IL-2 are activated CD4+ and CD8+ T cells. HIV-1 interactions implicate the gradual loss of IL-2 secretion and proliferation. It is an early sign of T cell exhaustion in HIV-1 infection. T-helper type 1 (Th1) cytokines such as IL-2 and the antiviral IFN-γ decrease during the course of HIV-1 infection [11]. IL-2 can simultaneously activate T effector cells and Foxp3 (+) Treg populations. It confers resistance to severe TB without enhancing *M. tuberculosis* infection. IL-2-producing Mtb-specific CD4 T cells Th1 cytokines IFN-γ and/or TNF-α are associated with individuals with latent tuberculosis. The Mtb containment high proportion of Mtb-specific CD4 T cells producing Th1 cytokines in the absence of IL-2 are associated with patients suffering from active TB disease [12]. HIV/TB co-infected patients of TB latency targeted by HIV-1 infection, resulting in early peripheral depletion of MTB-specific CD4+ T cells after HIV infection. Anti-tubercular treatment (ATT) associated with changes in the phenotype of Mtb-specific CD4 T cells with decreased expression of HLA-DR and increased CD27 and CD153 expression [13]. Polyfunctional T cell responses of IFN-γ (+) IL-2 (+) TNF-α (+) to TB antigens has been observed in HIV-1-infected patients dependent on their TB status, CD4 counts, and anti-retroviral exposure [14].

Interleukin-4 (IL-4) role. IL-4 is a cytokine that stimulates the proliferation of activated B-cells. It induces differentiation of naive helper T cells (Th0 cells) to Th-2 cells. IL-4 stimulates the expression of all HIV-1 isolates via a transcriptional activation mechanism. HIV infection functionally impairs *Mycobacterium tuberculosis*-specific CD4 and CD8 T-cell responses. HIV infection significantly reduced the Th2 (interleukin 4 [IL-4]/IL-5/IL-13) producing *M. tuberculosis*-specific CD4 T cells [15]. Blocking IL-4 cause significantly neutralized Mycobacterium containment and CD4+ IFNγ+ levels Treg expression. IL-4 can subvert mycobacterial containment in human macrophages, probably via perturbations in Treg and Th1-linked pathways [16].

Interleukin-6 (IL-6) role. IL-6 interleukin acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. IL-6 is secreted by macrophages in response to specific microbial molecules, referred to as pathogen-associated molecular patterns (PAMPs). In HIV-1 antibody positive patients, no correlation between IL-6 concentrations and CD4 positive cell numbers but a correlation with IgG. HIV-induced IL-6/IL-10 dysregulation of CD4 cells is associated with defective B cell help and autoantibody formation against CD4 cells [17]. In anti-TB treatment, a reduction in the percentage of CD4+ T cells showed a significant restoration similar to that of controls. Moreover, after intensive anti-TB treatment, serum levels of IL-1β, soluble interleukin-2 receptor, IL-6, and tumour necrosis factor-α were significantly decreased compared with before treatment [18]. The HIV envelope glycoprotein gp160 support B cell differentiation. T cell dependence for gp160-induced B cell differentiation responses requires contact-dependent interaction of several cell surface molecules and IL-6 secretion [19].

Interleukin-10 (IL-10) role. IL-10 is an anti-inflammatory cytokine, which is primarily produced by monocytes, and lesser extent by type-IIT helper cells (TH2) lymphocytes, mast cells, CD4+CD25+Foxp3+ regulatory T cells and certain subset of activated T cells and B cells. The inhibitory effects of IL-10 on HIV-1 replication become more pronounced in late stages of disease when CD4+ lymphocytes are depleted and replication in macrophages and monocytes. Interleukin-10 induced by human immunodeficiency virus type 1 and its gp120 protein in human monocytes/macrophages. Interleukin-10 influenced promoter polymorphisms on HIV-1 susceptibility pathogenesis and play a role by transcriptional regulation [20-22].

HIV induces the immunosuppressive IL-10 production in monocytes that interferes with HIV entry through CD4 molecules. IL-10 is a more potent inhibitor than TGF-β for both T-cell subsets CD4 (+) and CD8 (+) T-cell responses to *M. tuberculosis* infection control [23].

IL 10 production by macrophages and T-cells during the course of Mtb is observed to increase CD4 T cell counts and suppression of HIV viral load for all patients under HAART and TB treatment. Descendent trajectories were observed for the activated CD8 (+)/CD38 (+) and CD3 (+)/HLA-DR (+) T cell subsets, and for plasma concentration of gamma- interferon

(IFN-γ) in tuberculosis and HIV-positive individuals during antituberculous treatment [24].

Interleukin-12(IL-12) role. IL-12 is a naturally produced by dendritic cells, macrophages, neutrophils, and human B-lymphoblastoid. IL-12 family is unique heterodimeric cytokines, which includes IL-12, IL-23, IL-27 and IL-35. HIV-1 infection dysregulate regulatory pathways are characterized by decreased production of IL-12 and IFN-γ pro-inflammatory cytokines. The inhibition of IL-12 production by accessory cells after HIV-1 infection has been identified as a potential factor responsible for impaired innate and Th1 cell-mediated responses in AIDS patients. There was found a decreased CD40 ligand in CD4 T cells dependent IL-12 production in HIV-1 infection [25]. Human IL-12 and IL-23 are both required for optimal IFN-γ-dependent immunity to mycobacteria [26]. Systemic immune activation is critical to the pathogenesis of HIV-1 disease, and is accentuated in HIV/TB co-infected patients. The contribution of immune activation at sites of HIV/TB co-infection to viral activity, CD4 T cell count, and productive HIV-1 infection were measured markers of immune activation both in pleural fluid and plasma in HIV/TB co-infected subjects.

Interleukin-15 (IL-15) role. IL-15 is a cytokine similar to IL-2. IL-15 binds to signals through IL-2/IL-15 receptor beta chain (CD122) and the common gamma chain (gamma-C, CD132). IL-15 is secreted by mononuclear phagocytes. IL-15 regulates susceptibility of CD4 + T cells to HIV infection. IL-15 level was significantly elevated viral loads in HIV-1 infected patients compared to uninfected controls, suggesting a significant direct correlation between IL-15 and HIV-1 viraemia and an inverse correlation between IL-15 levels and CD4+ T cell counts [27]. NK cells produce not only IFN-γ but also IL-22 induced by IL-15 and DAP-10. Many invariant natural killer T (iNKT) cells are CD4+ and few iNKT cells are CD8+. Other iNKT cells are negative for both CD4 and CD8. Gamma Delta (γδ) T cells represents an early innate defense anti-mycobacterial immunity [28]. As NK cells are a significant source of the bactericidal effector molecule granulysin, infection of PBMC (peripheral blood mononuclear cell) with HIV-1 suppresses NK cell induction of granulysin by IL-15, but does not impair activation by BCG. This study suggests that HIV impair the anti-bacterial function of NK cells and have implications for clinical use of IL-15 to augment innate cell mediated immunity in HIV positive patients [29].

Interleukin-17 (IL-17) role. IL-17 is a pro-inflammatory cytokine. IL- 17 is a unique CD4+ T (Th17) cell subset play a role in host defense. Th17 cells are lost during HIV infection, although there is also a beneficial role of HIV-specific CD4 cells. Patients with lower immune activation exhibited higher frequency of bulk CD4 T-cells producing IFN-γ or IL-17 which change higher effector-to-regulatory cell ratios [30, 31]. Although initial studies suggested that γδ T cells are a primary source of IL-17 in response to *M. tuberculosis* infection [32]. Th17 cells are the major IL-17–producing cells and participate in the protective immunity against *M. tuberculosis*. The high proportion of CD4 (+) IFN-γ (+) IL-17(+) cells were detected in low responder TB patients with severe pulmonary lesions [33]. The cytokine frequency and polyfunctionality profile of *Mycobacterium tuberculosis* (MTB)-specific CD4+ T cells in HIV-infected persons with latent TB infection (LTBI) or Pulmonary TB (PTB) is comparable. This similarity suggests that LTBI represent a smoldering state of persistent MTB replication rather than dormant infection [34].

Interleukin-18 (IL-18) role. IL-18 is a pro-inflammatory cytokine. It is also known as IFN-γ inducing factor. Both hematopoietic cells and non-hematopoietic cells have the potential to produce IL-18. IL-18 brings an alteration in the immune response to tuberculosis (TB). Mycobacterial antigen-induced production plasma levels of inflammatory cytokine IFN-γ and its regulatory cytokines IL-18, and IL-12, IL-10 in HIV co-infected with TB patients. Patients with multidrug-resistant TB (MDRTB) have dysregulated IL-12, IL-18 and IL-10 production during *Mycobacterium tuberculosis*.

Interleukin-22 (IL-22) role. HIV infection indicates a gradual loss of CD4+ T-cells with progressive impairment of immunity lead ultimately to death. Study of IL-22+ cells of HIV-1 co-infected with *Mycobacterium tuberculosis* patients detect the levels of peripheral blood membrane-bound IL-22+ T cell subsets. Antigen-specific membrane-bound IL-22+ T cells are highly expressed in MTB co-infection of HIV-1 infected individuals, and play an important role in anti-TB immune response during co-infection with HIV-1 [35]. In multidrug-resistant TB (MDR-TB), low systemic and Mtb-induced Th22 responses associated with a high sputum bacillary load and bilateralism of lung lesions, suggesting that Th22 response could be influencing the ability of MDR-TB patients to control bacillary growth and tissue damage. The level of IL-22 and IFN-γ were significantly lower in the pleural fluid of HIV-1 co-infected TB than the TB patients. Antigen-specific membrane-bound IL-22+ T cells are highly expressed in MTB co-infection of HIV-1 and play anti-TB immune response. Proteomics analyses revealed the enrichment of HIF-1α, galectins and Hsp90 host factors, which promoted HIV-1 reactivation *M. tuberculosis*-specific exosomes [36]. Tuberculosis (TB) and AIDS are the leading causes of death, but in some TB-HIV co-infected individuals treated for both diseases simultaneously, an inflammatory reaction termed immune reconstitution inflammatory syndrome (IRIS) occur.

Interleukin-27 (IL-27) role. IL-27 is a heterodimeric cytokine and a member of the IL-12 family. IL-27 has been shown to be a potent inhibitor of HIV-1 infection in CD4+ T cells and macrophages. IL-27 treated dendritic cells (DCs) have shown highly potent inhibitors of HIV-1, whereas IL-12, IL-23 and IL-35 have no effect on HIV-1 replication. IL-27-producing CD4 (+) T cells represent a distinct T cell subset in tuberculosis pleural effusion (TPE). Both the numbers of IL-27-producing CD4 (+) T cells and concentration of soluble IL-27 have been found to be increased in tuberculous pleural effusion (TPE). In HIV-infected, the plasma IL-27 level correlates positively with CD4+ T-cell count and negatively with HIV- viral load. IL-27 in HIV- *M. tuberculosis* co-infection acts on MDSC both in autocrine and paracrine manner. HIV-infected individuals with virologic suppression have increased levels of circulating IL-27 and myeloid-derived suppressor cells (MDSC). IL-27/IL-27R and MDSC provide attractive biomarkers to assess tuberculosis prognosis during HIV-infection [37].

Interleukin-32 (IL-32) role. IL-32 is inflammatory and clinical markers, expressed during HIV-1 infection in CD4+ T cells, B cells, macrophages, and dendritic cells. Increased expression of IL-32 seen with IFN-γ, Th1 and Tc1 in virologically suppressed HIV-1-infected patients. IL-32 is highly expressed in the mucosal epithelium of HIV-1- infected gut. IL-32's action on IFN-γ and IFN-γ secreting T cell subsets help sustain the immune activation and dysregulation found in patients with HIV-1 achieving viral suppression. Both IL-32 and IFN-γ genes were also more strongly expressed in CD4+ T cells than in CD14+ monocytes. IL-32 levels remain elevated in treating HIV-1-infected patients [38].

Interleukin-35 (IL-35) role. IL-35 is anti-inflammatory cytokine from the IL-12 family. IL-35 is produced by a wide range of regulatory

lymphocytes and plays a role in immune suppression. IL-35 can block the development of Th1 and Th17 cells by limiting early T cell proliferation. Little is known for IL-35 response in patients with active tuberculosis (ATB). Active tuberculosis patients exhibited increases in serum IL-35 and in mRNA expression of both subunits of IL-35 (p35 and EBI3) in white blood cells and peripheral blood mononuclear cells. TB infection was associated with expression of p35 or EBI3 protein in CD4 (+) but not CD8 (+) T cells. Most p35 (+) CD4 (+) T cells and EBI3 (+) CD4 (+) T cells expressed Treg-associated marker CD25. IL-35 in the blood serves as a biomarker for immune status and prognosis in TB [39].

Immune mechanism in HIV co-infection Tuberculosis therapy

Tuberculosis is a serious health threat, especially for people living with HIV. HIV virus increases the potency of the tuberculosis bacterium (Mtb) by affecting a central function of the immune system. In HIV infected individuals, CD38 and HLA-DR on CD4 and CD8 T lymphocytes are elevated immune reconstitution inflammatory syndrome (IRIS). In response to antiretroviral therapy-mediated recovery of the immune system in HIV-infected patients, it was seen effects of initiating efavirenz (EFV) or raltegravir (RAL)-based antiretroviral therapy (ART) regimens HIV-1 deoxyribonucleic acid (DNA) levels and inflammation biomarkers in the highly inflammatory setting of advanced HIV-1 disease with tuberculosis (TB) co-infection [40].

TB treatment in HIV-TB co-infected persons have a prolonged duration due to the immune system fails to provide an adequate support for the therapy. 7-oxo-DHEA modifies the cytokine balance and the phenotype of CD4 + T cells more favorable to mycobacteria control where novel treatment approaches as co-adjuvant for the treatment of TB [41]. Thalidomide, which inhibits monocyte TNF-α production and co-stimulates T cells, was tested for immune modulation in patients with human immunodeficiency virus HIV infection and TB. Thalidomide therapy resulted in increased levels of plasma IL-2 receptor, soluble CD8, IFN-γ, and IL-12. Thalidomide treatment increased CD4+ and CD8+ T cell counts and increased viral replication [42].

Combination antiretroviral therapy in tuberculosis (TB) and HIV-1 infection is associated with an immune reconstitution inflammatory syndrome (TB-IRIS). In serum, higher concentrations of TNF, IL-6, and IFN-γ were observed with TB-IRIS patients. Serum IL-6 and TNF-α decreased during prednisone therapy in TB-IRIS patients. It also showed increased IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p40, IFN-γ, GM-CSF and TNF in TB-IRIS cultures in peripheral blood mononuclear cell culture in the presence of heat-killed *Mycobacterium tuberculosis* [43].

HIV-1 patients co-infected with some pathogens are at risk of developing the IRIS when initiating antiretroviral therapy (ART). HIV-TB co-infected patients prescribed with anti-tuberculosis treatment and ART develop TB-IRIS [44].TB-IRIS patients and controls had similar CD4 counts, levels of T-cell-associated immune activation, and frequencies of IFN-γ(+)/IL-2(+)/TNF-α(+),CD4(+) T-cells prior to ART initiation. After ART initiation, cellular immune activation and T-cell subsets also were similar in TB-IRIS patients and controls. In contrast, TB-IRIS patients had significantly greater early increases in the IFN-γ (+)/IL-2 (+)/TNF-α (+)CD4(+) T-cells in ART and increases IL-6 is associated with the development of paradoxical TB-IRIS [45].

There is a high prevalence of drug-resistant mutations in HIV and HIV-TB co-infected patients. In the HIV-TB group had mutations to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs), respectively. Silencing of the expression of the nuclear factor of activated T cells 5 (NFAT5) by RNA interference (RNAi) inhibits *Mycobacterium tuberculosis* (MTb)-stimulated HIV-1 replication in co-infected macrophages. NFAT5 gene and protein expression are strongly induced by MTb, which is a Toll-like receptor (TLR) ligand RNAi key components of the TLR pathway in human monocytes, including the downstream signaling molecules MyD88, IRAK1, and TRAF6, significantly inhibits MTb-induced NFAT5 gene expression [46]. SOCS1 factor or IL-27 down-regulate the IFN-γ/IL-12 axis, thereby impairing control are mainly anti-inflammatory but indirectly inhibit efficient bacterial clearance. Increased replication of the virus was demonstrated in the lungs and within activated lymphocytes and CD14+ macrophages of the pleural space in *M. tuberculosis* infection. The suppressor of cytokine signaling 1 (SOCS1) is an inducible host factor during HIV-1 infection and regulates the late stages of the HIV-1 replication pathway. The function of many immune cells, including macrophages and DCs, is modulated by both HIV and *M. tuberculosis*. Increased replication of the virus was demonstrated locally, at sites of *M tuberculosis* infection in the lung, and within activated cells, including lymphocytes and CD14 + macrophages, of the pleural space of co-infected patients [47, 48].

Impaired balance between pro-inflammatory and anti-inflammatory cytokines and apoptosis-induced depletion of immune effector cells accounts for the dissemination of both the pathogens and for a poor granulomatous reaction in Mtb-HIV co-infected patients [49]. Patients with HIV-associated tuberculosis (TB) initiating antiretroviral therapy (ART) develop an immune reconstitution inflammatory syndrome (TB-IRIS), the signature is characterized by over-representation of TLR signalling and TREM-1 activation of the inflammasome. Inhibition of MyD88 adaptor and group 1 caspases reduces secretion of IL-1 in TB-IRIS patients [50].

Conclusion

Various cytokines play different roles in HIV-1 and TB individually and in a co-infection stage of disease during infection. IL-2 play CD4+ proliferation, IL-4 activate B cells, CD4 cell IL-6/IL-10 dysregulate in HIV-1, CD4+ T (Th17) cell subset lost during HIV-1, IL-22 and IL-27-producing CD4(+) T cells represent a distinct Tcell subset in tuberculous pleural effusion (TPE). It was seeing the effects of initiating efavirenz (EFV) or raltegravir (RAL)-based antiretroviral therapy (ART) regimens on human immunodeficiency virus (HIV)-1 deoxyribonucleic acid (DNA) levels and inflammation biomarkers in the highly inflammatory setting of advanced HIV-1 disease with tuberculosis (TB) co-infection. HIV co-infected TB patients have prolonged treatment duration due to the immune system failing to provide support for the therapy. HIV co-infected TB patients have mutations to nucleoside reverse transcriptase, inhibits MTb-induced NFAT5 gene expression. It was noted that bacteria are not completely eradicated despite of a seemingly robust Th1 immune response in the latent phase of tuberculosis. A failure of the protective adaptive immune responses leads to reactivation of infection.

Acknowledgements

Gratefully acknowledged to Dr. V. K. Mahadik, Director, and R. D. Gardi Medical College for the encouragements, and to establish and develop research in biomedical sciences.

References

1. Getahun H, Gunneberg C, Granich R, Nunn P (2010) HIV infection-associated tuberculosis: the epidemiology and the response. *Clinical Infectious Diseases* 50: Suppl 3S201–S207
2. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH et al. (1989) A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *New England Journal of Medicine* 320: 545–550.
3. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M et al. (1995) Accelerated course of human immunodeficiency virus infection after tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 151: 129–135.
4. Modjarrad K, Vermund SH (2010) Effect of treating co-infections on HIV-1 viral load: a systematic review. *Lancet Infectious Diseases* 10: 455–463.
5. Lazarevic V, Flynn J (2002) CD8+ T cells in tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 166: 1116–1121.
6. Orme IM, Roberts AD, Griffin JP, Abrams JS (1993) Cytokine secretion by CD4 T lymphocytes acquired in response to Mycobacterium tuberculosis infection. *Journal of Immunology*151 (1):518–525.
7. Moir S, Chun TW, Fauci AS (2011) Pathogenic mechanisms of HIV disease. *Annual Review of Pathology* 6: 223–248.
8. Geijtenbeek TB, Van Vliet SJ, Koppel EA, Sanchez-Hernandez M, Vandenbroucke-Grauls CM et al. (2003) Mycobacteria target DC-SIGN to suppress dendritic cell function. *Journal of Experimental Medicine* 197: 7–17.
9. Lawn SD, Bekker LG, Miller RF (2005) Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infectious Diseases* 5: 361–373.
10. Breton G, Duval X, Estellat C, Poaletti X, Bonnet D et al. (2004) Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clinical Infectious Diseases* 39: 1709–1712.
11. Kedzierska K, Crowe SM (2001) Cytokines and HIV-1: interactions and clinical implications. *Antiviral Chemistry & Chemotherapy* 12(3):133-150. Review.
12. Wang X, Zhang J, Liang J, Zhang Y, Teng X et al. (2015) Protection against Mycobacterium tuberculosis infection offered by a new multistage subunit vaccine correlates with increased number of IFN-γ+ IL-2+ CD4+ and IFN-γ+ CD8+ T cells *PLoS One* 10(3):e0122560.
13. Riou C, Bruyn ED, Ruzive S, Goliath RT, Lindestam Arlehamn, CS et al. (2020) Disease extent and anti-tubercular treatment response correlates with Mycobacterium tuberculosis-specific CD4 T-cell phenotype regardless of HIV-1 status. *Clinical and Translational Immunology.* 9(9):e1176.
14. Sutherland J S, Young J M, Peterson K L, Sanneh B, H C Whittle H C (2010) Polyfunctional CD4(+) and CD8(+) T cell responses to tuberculosis antigens in HIV-1-infected patients before and after anti-retroviral treatment. *Journal of Immunology* 184(11):6537-6544.
15. Amelio P, Portevin D, Hella J, Reither K, Kamwela L et al (2019) HIV Infection Functionally Impairs Mycobacterium tuberculosis-Specific CD4 and CD8 T-Cell Responses. *Journal of Virolology* 93(5):e01728-18.
16. Pooran A, Davids M, Nel A, Shoko A, Blackburn J et al. (2019) IL-4 subverts mycobacterial containment in Mycobacterium tuberculosis-infected human macrophages. *European Respiratory Journal* 54(2):1802242. doi: 10.1183/13993003.02242-2018.
17. Weimer R, Zipperle S, Daniel V, Zimmermann R , Schimpf, K et al. (1998) HIV-induced IL-6/IL-10 dysregulation of CD4 cells is associated with defective B cell help and autoantibody formation against CD4 cells. *Clinical and Experimental Immunology* 111(1): 20–29.
18. Luo X, Wu F, Ma J, Xiao H, Cui H (2018) Immunological recovery in patients with pulmonary tuberculosis after intensive phase treatment. *Journal of International Medical Research* 46(9):3539-3551
19. Chirmule N, Kalyanaraman V S, Lederman S, Oyaizu N, Yagura H (1993) HIV-gp 160-induced T cell-dependent B cell differentiation. Role of T cell-B cell activation molecule and IL-6. *Journal of Immunology* 150(6):2478-2486.
20. Borghi P, Fantuzzi L, Varano B, Gessani S, Puddu P (1995) Induction of interleukin-10 by human immunodeficiency virus type 1 and its gp120 protein in human monocytes/macrophages. *Journal of Virology* 69(2): 1284–1287.
21. Naicker DD, Werner L, Kormuth E, Passmore JA, Mlisana K (2009) Interleukin-10 Promoter Polymorphisms Influence HIV-1 Susceptibility and Primary HIV-1 Pathogenesis. *Journal of Infectious Diseases* 200(3): 448–452.
22. Iyer SS, Cheng G (2012) Role of Interleukin 10 Transcriptional Regulation in Inflammation and Autoimmune Disease. *Critical Reviews in Immunology* 32(1): 23–63.
23. Rojas RE, Balaji KN, Subramanian A, Boom WH (1999) Regulation of human CD4(+) alphabeta T-cell-receptor-positive (TCR(+)) and gammadelta TCR(+) T-cell responses to Mycobacterium tuberculosis by interleukin-10 and transforming growth factor beta. *Infection and Immunity* 67(12): 6461-6472
24. da Silva TP, Giacoia-Gripp CBW, Schmaltz CA, Sant Anna FM, Rolla V et al. (2013) T Cell Activation and Cytokine Profile of Tuberculosis and HIV-Positive Individuals during Antituberculous Treatment and Efavirenz-Based Regimens. *PLoS One* 8(6):e66095.
25. Ma X, Montaner, LJ (2000) Proinflammatory response and IL-12 expression in HIV-1 infection. *Journal of Leukocyte Biology* 68(3): 383-390.
26. Martínez-Barricarte R, Markle JG, Ma CS, Deenick EK, Ramírez-Alejo N et al. (2018) Human IFN-γ immunity to mycobacteria is governed by both IL-12 and IL-23. *Science Immunology* 3(30):eaau6759.
27. Manganaro L, Hong P, Hernandez MM, Argyle D, Mulder LC et al. (2018) IL-15 regulates susceptibility of CD4 + T cells to HIV infection. *Proceedings of the National Academy of Sciences of the United States of America.* 115(41):E9659-E9667.
28. Zhang Q, Sugawara I (2012) Immunology of tuberculosis. *World Journal of Experimental Medicine* 2(4): 70-74.
29. Hogg A, Huante M, Ongaya A, Williams J, Ferguson M et al. (2011) Activation of NK cell granulysin by mycobacteria and IL-15 is differentially affected by HIV. *Tuberculosis* (Edinb) 91 Suppl 1: S75-81.
30. Chevalier MF, Didier C, Girard PM, Manea ME, Campa P (2016) CD4 T-Cell Responses in Primary HIV Infection: Interrelationship with Immune Activation and Virus Burden. *Frontiers in Immunology* 7:395.
31. Bhopale MK, Shah H, Bamboria BL, Julka A, Patel I et al. (2019) Cytokine Responses in the Blood and Pleural Fluid of Pulmonary Tuberculosis Patients with and without HIV-1 Co-infection *Journal of Biotechnology and Biomedicine* 2 (3): 057-066 DOI: 10.26502/jbb.2642-91280010.
32. Lyadova IV, Panteleev AV (2015) Th1 and Th17 Cells in Tuberculosis: Protection, Pathology, and Biomarkers. *Mediators of Inflammation* 2015:854507. Review

33. Jurado J O, Pasquinelli V, Alvarez I B, Peña D, Rovetta A I et al. (2012) IL-17 and IFN-γ expression in lymphocytes from patients with active tuberculosis correlates with the severity of the disease. *Journal of Leukocyte Biology* 91(6): 991-1002.
34. Canaday DH, Sridaran S, Van Epps P, Aung H, Burant C J et al. (2015) CD4+ T cell polyfunctional profile in HIV-TB coinfection are similar between individuals with latent and active TB infection. *Tuberculosis* (Edinb) 95(4):470-475.
35. Liu Q, Yu C, Cheng J, Jiang Y, Xu Y et al. (2021) Characterization of membrane-bound IL-22+ T cell subsets in HIV-1 patients coinfected with Mycobacterium tuberculosis. Journal of Microbiology, *Immunology and Infection* 54 (3):429-436.
36. Tyagi P, Pal VK, Agrawal R, Singh S, Srinivasan S et al. (2020) Mycobacterium tuberculosis Reactivates HIV-1 via Exosome-Mediated Resetting of Cellular Redox Potential and Bioenergetics. *mBio* 11(2):e03293-19.
37. Namdev P, Patel S, Sparling B, and Garg A. (2021) Monocytic-Myeloid Derived Suppressor Cells of HIV-Infected Individuals With Viral Suppression Exhibit Suppressed Innate Immunity to Mycobacterium tuberculosis. *Frontiers in Immunology* 12: 647019.
38. Santinelli L, Statzu M, Pierangeli A , Frasca F, Bressan A, et al. (2019) Increased expression of IL-32 correlates with IFN-γ, Th1 and Tc1 in virologically suppressed HIV-1-infected patients. *Cytokine* 120: 273-281
39. Kong B, Liu GB, Zhang JA, Fu XX, Xiang WY et al. (2016) Elevated serum IL-35 and increased expression of IL-35-p35 or -EBI3 in CD4(+)CD25(+) T cells in patients with active tuberculosis. *American Journal of Translational Research* 8(2): 623-633.
40. Delagreverie HM, Bauduin C, De Castro N, Grinsztejn B, Chevrier M et al. (2020) Impact of Raltegravir or Efavirenz on Cell-Associated Human Immunodeficiency Virus-1 (HIV-1) Deoxyribonucleic Acid and Systemic Inflammation in HIV-1/Tuberculosis Coinfected Adults Initiating Antiretroviral Therapy. *Open Forum Infectious Diseases* 7(2): ofz549.
41. Vecchione MB, Laufer N, Sued O, Corti M, Salomon H et al. (2020) 7-oxo-DHEA enhances impaired M. tuberculosis-specific T cell responses during HIV-TB coinfection. *Journal of Biomedical Science* 27(1):20.
42. Bekker LG, Haslett P, Maartens G, Steyn L, Kaplan G (2000) Thalidomide-induced antigen-specific immune stimulation in patients with human immunodeficiency virus type 1 and tuberculosis. J*ournal of Infectious Diseases* 181(3):954-965.
43. Tadokera R, Meintjes G, Skolimowska KH, Wilkinson KA, Matthews K et al. (2011) Hypercytokinaemia accompanies HIV-tuberculosis immune reconstitution inflammatory syndrome. *European Respiratory Journal* 37(5):1248-1259.
44. Lai RPJ, Nakiwala JK, Meintjes G, Wilkinson, RJ (2013) The immunopathogenesis of the HIV tuberculosis immune reconstitution inflammatory syndrome. European *Journal of Immunology*. 43(8):1995-2002.
45. Ravimohan S, Tamuhla N, Nfanyana K, Steenhoff AP, Letlhogile R et al. (2016) Robust Reconstitution of Tuberculosis-Specific Polyfunctional CD4+ T-Cell Responses and Rising Systemic Interleukin 6 in Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. *Clinical Infectious Diseases* 62(6):795-803.
46. Ranjbar S, Jasenosky LD, Chow N, Goldfeld AE (2012) Regulation of Mycobacterium tuberculosis-dependent HIV-1 transcription reveals a new role for NFAT5 in the toll-like receptor pathway. *PLOS Pathogens* 8(4):e1002620.
47. Ryo A, Tsurutani N, Ohba K, Kimura R, Komano J et al. (2008) SOCS1 is an inducible host factor during HIV-1 infection and regulates the intracellular trafficking and stability of HIV-1 Gag. *Proceedings of the National Academy of Sciences of the United States of America* 105(1): 294-299.
48. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G (2012) Tuberculosis and HIV Co-Infection *PLoS Pathogens* 8(2): e1002464..
49. Bocchino M, Sanduzzi A, Bariffi F (2000) Mycobacterium tuberculosis and HIV co-infection in the lung: synergic immune dysregulation leading to disease progression. *Monaldi Archives for Chest Disease* 55(5):381-388.
50. Lai RPJ, Meintjes G, Wilkinson KA, Graham CM, Marais S, der Plas HV et al. (2015) HIV-tuberculosis-associated immune reconstitution inflammatory syndrome is characterized by Toll-like receptor and inflammasome signaling. *Nature Communications* 6:8451.doi: 10.1038/ncomms9451.

DOI: 10.31579/IJBR-2021/034