REVIEW

# CHALLENGES FACED BY THE IMMUNE RESPONSE TOWARDS HIV AND *Mycobacterium tuberculosis* CO-INFECTION*

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## SUMMARY

*Mycobacterium tuberculosis* is responsible for an extremely important life-threatening disease, which affects approximately one third of the world's population. Tuberculosis (TB) claims more lives than any other single infectious disease. Despite the availability of the Bacille Calmette-Guérin (BCG) vaccine and the widespread implementation of Directly Observed Short-Course (DOTS), TB has emerged as a major complication of HIV infection in both developing and industrialized countries. Using different pathways, *M. tuberculosis* infects macrophages, its preferential habitat, which paradoxically are the chief effector cells for killing mycobacteria. The balance between these functions determines the outcome of infection. As an intracellular pathogen, protective immunity to *M. tuberculosis* requires Cell-Mediated Immunity (CMI), which major effector mechanism is the activation of infected macrophages by type-1 cytokines, particularly interferon-γ, produced primarily by Th-1 $CD4^+$ lymphocytes, in response to macrophage products, such as interleukin-12. Cytotoxic T Lymphocyte (CTL) response mediated by CD8 + cells also participate in effective CMI against mycobacteria. Human Immunodeficiency Virus (HIV) infection is detrimental to *M. tuberculosis*-infected patients increasing the risk for both primary and reactivation TB, and for second episodes of TB from exogenous re-infection. The immunological explanation has become evident: both pathogens require Th-1 type response, which is compromised in both infections. TB has also had a great impact on HIV: HIV replicates more efficiently in activated T cells and viral levels increase consistently when the immune system is activated by exogenous stimuli, such as *M. tuberculosis*. The increase in viral replication is associated with cytokines released by the activated macrophage, particularly tumor necrosis factor-α and interleukin-1. *M. tuberculosis* also induces nuclear factor kappa-B, a cellular factor that binds to promoter regions of HIV, enhancing its replication. Early identification of HIV-TB coinfection is crucial for prompt anti-mycobacterial and anti-retroviral therapeutic

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interventions, before deterioration of the immune system occurs, resulting in improved survival of the patients.

KEYWORDS: HIV/AIDS. *Mycobacterium tuberculosis.* HIV/TB co-infection. Immune response.

## 1. The Scenario of Tuberculosis and HIV Infection in the World

Tuberculosis (TB), an ancient scourge of humankind, is responsible for countless millions of deaths worldwide and continues to kill about 3 million people every year. Mortality due to TB alone is higher than demises associated with any other infectious agent (45). One third of the world's population is estimated to be latently infected by *M. tuberculosis*, 5 to 10% of them may develop active TB disease at some point in their lives (28).

The advances in basic and applied research of *M. tuberculosis* are noteworthy. More than a century after its discovery by Robert Koch and fifty years after Dicken's publication about TB as "a disease which medicine never cured" (16), its complete genome sequence was deciphered (12). This hallmark study has broadened our understanding about the biology of *M. tuberculosis* and will surely lead to new strategies for prophylaxis and treatment.

According to the World Health Organization (WHO) 3.8 million TB cases were reported in 1996, Brazil figuring with the sixth highest incidence coefficient ($54.7 \times 10^5$). A total of 83,309 TB cases were reported to the Brazilian Ministry of Health in 1997, with an incidence coefficient of $51.7 \times 10^5$ (43). In 1995, the city of Rio de Janeiro showed a TB incidence coefficient of $160 \times 10^5$ (13), similar to what has been observed in some African countries, where TB is highly endemic.

Control of TB should involve prevention with an effective vaccine together with improved diagnosis and treatment. One of the first and oldest vaccines for humans is the Bacille Calmette and Guérin, BCG. It is one of the most common vaccines used in developing countries, designed to protect against TB but also demonstrated to be effective against leprosy (34). For TB, the overall efficacy of BCG ranges from no protection to 80% protection (8). TB vaccine trials in the United Kingdom provided more than 70% protection, whereas in South India, no significant protection was observed (70). Interestingly, in South India, leprosy vaccine trials with BCG have shown protective efficacy around 25%, with best protection observed in youngest age groups (32).

The BCG was derived from an isolate of *Mycobacterium bovis* which causes bovine tuberculosis. Initially, between 1908 and 1921, BCG was attenuated by 230 *in vitro* laboratory passages. Until the introduction of lyophilized BCG vaccines by 1960s, the live vaccine required additional



continued passages, approximately 1000 times, eventually resulting in a mixture of different phenotypes of daughter strains which collectively constitute the BCG. Recently, Behr et al. (2) compared the genomes of BCG strains with that of *M. tuberculosis* and *M. bovis* strains using comparative hybridization to a DNA microarray. The authors demonstrated that BCG strains from different parts of the world have undergone a series of deletions in their genomes, to adapt themselves to environmental changes, e.g., the laboratory passages required to maintain the mycobacteria alive. The authors suggest that this may explain the variation in BCG efficacy around the world. Another possible explanation for the declining BCG efficacy has been recently proposed (60) and that is the concurrent evolutionary changes undergone by *M. tuberculosis* during *in vivo* passages over the years, probably due to selective pressure favoring adaptation of the microorganism to BCG-induced immunity. New approaches for vaccine development such as DNA vaccination, use of secreted or surface-exposed proteins as immunogens, recombinant BCG or attenuated *M. tuberculosis* have been proposed (69).

Effective TB treatment is available at relatively low cost. Nevertheless, increased incidence of TB has been observed in both developing and industrialized countries. Widespread emergence of drug resistant strains and a sinister sinergy between this ancient disease and a new emergent pathogen, the Human Immunodeficiency Virus (HIV) have arisen. The WHO's Global Tuberculosis Program declared TB as a global health emergency and has promoted widespread implementation of the Directly Observed Therapy Short-course (DOTS), aimed to assure that all patients receive a full course of standardized short-course chemotherapy, which means essentially, 6 months of intermittent supervised therapy (63).

Despite some good results, DOTS have not been implemented in many countries with high TB prevalence rates and has not been able to control TB in countries with highest rates of HIV infection. The HIV pandemic has precluded the elimination of TB in the industrialized countries and prevented infection rates from falling in the developing world.

According to the WHO, there are 33.4 million people infected by HIV around the world, with an estimated 22.5 million infected in sub-Saharan Africa, 6.7 million in South and Southeast Asia, 1.4 million in Latin America, and 665,000 in United States (67). Brazil has the fifth highest prevalence rate of HIV infection among all countries worldwide, with 570,000 estimated cases by 1997 and 155,590 reported AIDS cases by 1998 (42).

In Brazil, south and southeastern states concentrate the majority of AIDS cases. São Paulo and Rio de Janeiro states reported 74,075 and 23,664 cases to the Ministry of Health by 1998, respectively (42).

*M. tuberculosis* and HIV have similar geographic distribution, infect pivotal cells of the immune system, lead to slow-onset diseases and are shown to exacerbate each other. HIV is the strongest risk factor for the development of active TB disease (66). Because HIV is spreading in regions with the highest rates of *M. tuberculosis*, HIV has been responsible for an increasing proportion of the world's cases of TB. Nearly 6 million people in the world were estimated to be co-infected with HIV and *M. tuberculosis* in 1995, with 67% of them living in Africa, 23% in South-East Asia and 7.2% in Latin America and Caribbean. By the year 2000 it is estimated that HIV will be responsible for 14% of the active TB incident cases worldwide (15).

Moreover, TB is the most common opportunistic infection and the leading cause of death in persons infected with Human Immunodeficiency Virus (HIV) worldwide (62). Forty percent of all Acquired Immunodeficiency Syndrome (AIDS)-related deaths in Africa and Asia can be atributable to TB. In sub-Saharan Africa, where over 60% of children and 70% of adults are co-infected with HIV (23), mortality in dually infected individuals can be as high as 50% within a period of 18 months (24). In Brazil, by February/1999, 15.7% and 12.5% of all AIDS notified cases presented pulmonary and extra-pulmonary TB respectively as opportunistic diseases (42) with an estimation of 150,000 individuals being co-infected with HIV and *M.tuberculosis* (5).

2. *Mycobacterium tuberculosis*: Immunity and Immunopathology

The immune response to *M. tuberculosis* is not often sterilizing, and can lead to latent infection. The tubercle bacillus is an intracellular microorganism, with characteristic features that include slow growth, dormancy, complex cell envelope, and a generation time of approximately 24 hours. These characteristics contribute to the chronic nature of TB. Clinical disease occurs when mycobacterial replication can not be controlled after initial infection, primary TB, or when latent organisms are able to overcome immunologic control, considered as reactivation TB. Approximately 5% of immunological normal individuals, who become infected by *M. tuberculosis*, will develop primary TB within 2 years of initial infection, another 5% of exposed persons will reactivate TB at some point later in life (61).

Protective immunity to intracellular bacteria, such as *M. tuberculosis* has long been known to depend on cell-mediated immunity (CMI). The major effector mechanism of CMI is considered to be the activation of infected macrophages by type-1 cytokines, particularly INF-γ, which activates microbicidal mechanisms able to control and eliminate the intracellular bacteria. CMI may also involve cell-mediated lysis of infected macrophages by cytotoxic T cells and perhaps natural killer (NK cells) (51).



The development of immune resistance against TB depends upon a complex interplay between the pathogen and the host immune system. *M. tuberculosis* infection is acquired through inhalation of infectious airborne particles that reach the alveolar spaces, where they infect macrophages. In some individuals, alveolar macrophages may have a high degree of innate mycobacterial resistance, and in these persons the tubercle bacilli are presumably destroyed before infection is established. In other persons, the mycobacteria is able to survive phagocytosis, replicate and spread to regional lymph nodes and throughout the body (18).

Different stages of pulmonary TB disease can be observed. In the first stage the bacterium is inhaled and ingested by a macrophage. The process can end at this point if the bacterium is destroyed. In case the mycobacteria survives, it replicates and a second-stage with bacterium-loaded macrophages develops. A third stage occurs when the mycobacteria is walled off by a variety of immune effector cells, specially highly activated macrophages, including epithelioid and multinucleated giant cells. The continuing activation of macrophages leads to tissue necrosis and anoxia, through the release of macrophage products including reactive oxygen and nitrogen intermediates. Depending on the resistance/susceptibility immune status of the host, lesions may either regress with consequent destruction of bacteria within them, or the disease may progress with lesions going on to caseate and liquefy. The liquefied tissue is an excellent medium for mycobacterial growth, and the lung tissue disintegrates with the formation of cavities (14).

*M. tuberculosis* has developed numerous mechanisms for entering human macrophages. When opsonized, *M. tuberculosis* can use Fcγ and complement receptors (CR1, CR3, CR4). If not opsonized, they can use other receptors such as the CD14 molecule, mannose receptor, surfactant protein-A receptor or scavenger receptors (26). From the evidence available it does not seem that individual entry pathways have a major influence on intracellular survival and growth of the mycobacteria, but that *M. tuberculosis* tries hardly to get inside the macrophages, by different pathways. After ingesting the mycobacteria, macrophages process and present *M. tuberculosis* antigens to $CD4^+$ T cells, on the context of major histocompatibility complex (MHC) class II molecules. At this point, cytokines, soluble mediators of the immune response play a very important role. According to the cytokines they produce, $CD4^+$ T lymphocytes are classified into at least type 1 and type 2 cells, required for CMI and humoral immunity, respectively. T helper 0 (Th0) cells with unrestricted profile of cytokines have also been described (44,27).

Once infected with *M. tuberculosis*, macrophages start secreting interleukin –1 (IL-1), which drives interleukin-2 (IL-2) production and IL-2 receptor expression by $CD4^+$ T cells, which, in turn, are stimulated to proliferate. Macrophages also secrete interleukin-12 (IL-12) and interleukin-

18 (IL-18) (65). These cytokines have been shown to influence both innate and adaptive immune responses, favoring INF-γ production by NK and $CD4^+$ T cells, respectively (72). INF-γ promotes monocyte recruitment and maturation into macrophages with enhanced phagocytic and microbicidal activity. This pattern of response is typical of $CD4^+$ T helper cell type 1 (Th1) and it has been demonstrated to be effective in confining the mycobacteria in a localized inflammatory granuloma and restraining its growth through repeated cycles of phagocytosis, cytolysis, and exposure to microbicidal products (62) (Fig. 1).

Type 2 responses, characterized by IL-4 and IL-10 production, without cytotoxic function may be induced in TB and do not contribute to protection (6,50,73). Suppression of type-1 or a switch to type-2 profile is detrimental. The possibility of shifting the response towards type I profile might result in great benefit for the patient. In fact, helminthic infections are known to elicit a type-2 response and are very common in the developing countries. It has been recently suggested that large-scale eradication of helminthic infections in the developing world, a relatively simple and inexpensive process, may change the immune profile towards a Th-1 pattern, and may have a huge impact on TB epidemics (3).

INF-γ activates macrophages, converting them from a habitat to potent effector cells. INF-γ induces cellular activation by binding to a receptor complex consisting of at least two subunits: the INF-γ-binding subunit (INF-γ R1) and the INF-γ receptor signaling chain (INF-γ R2). Normal signal transduction requires both components, i.e., binding of INF-γ induces dimerization of INF-γ R1, which then associates with INF-γ R2 and a series of phosphorylation reactions take place to promote cellular activation (35). Patients with complete IFN-γ R1 deficiency have shown severe susceptibility to infection with mycobacteria and develop the disease very early, often fatal, before three years of age. They usually develop poorly differentiated mycobacterial granulomas characterized by the presence of dispersed macrophages and the absence of epithelioid and giant cells. Inside the macrophages, large numbers of acid-fast bacilli can be found, resembling the granulomas observed in lepromatous leprosy patients. In contrast to complete deficiencies, partial INF-γ R1 deficiencies have been associated with mature granulomas and a milder course of mycobacterial infection (reviewed in 53). Such deficiencies have been demonstrated in patients who are homozygous for a nucleotide mutation that leads to a threonine for isoleucine amino acid substitution (33). These patients exhibited paucibacillary, well-diferentiated, "tuberculoid-like" granulomas and responded well to TB chemotherapy. Complete INF-γ R2 genetic deficiency has been recently described in a three-year old patient (20) which clinically,



immunologically and histopathologically resembled IFN-γ R1 complete deficiency.

IL-12, another crucial citokine, promotes cell-mediated immunity to intracellular pathogens by inducing Th1 responses and INF-γ production. It is a heterodimeric cytokine that consists of two disulfide-linked subunits, p40 and p35, and is released by activated antigen presenting cells, i.e., macrophages and dendritic cells (64). The receptor for IL-12 is composed of two distinct subunits, β1 and β2, that are assembled to form a high-affinity IL-12 receptor (IL-12R) on T cells and NK cells (reviewed in 52). IL-12Rβ1 deficiencies have shown to be associated with impaired INF-γ production, but with a milder clinical phenotype, similar to patients with partial INF-γ R1 deficiencies. However, these patients show increased susceptibility to mycobacterial infections (7,52). DNA vaccines have been demonstrated to induce IL-12 production, which consequently leads to preferential acquisition of type-I phenotype, crucial for CMI in TB (36). Recently, *M. tuberculosis* DNA vaccination in mice, initially designed to prevent infection, has also shown therapeutic effect (37).

$CD8^+$ T cells also play a part in protective immunity against mycobacteria. Data from experimental models indicate that animals lacking $CD8^+$ T cells are much more susceptible to infection, specifically in the lungs (48). It has been suggested that the role of $CD8^+$ T cells is to lyse infected macrophages, either by the perforin/granzyme pathway or via CD95 ligation (reviewed in 4). However, recent data indicate that these lytic mechanisms do not contribute directly to the initial mechanisms of protection but seem to be important in controlling the chronic phase of the disease. In animal models, $CD8^+$ T cells have been shown to be a source of INF-γ and therefore may also be involved in macrophage activation (49).

T cells expressing the γδ T-cell receptor (TCR γδ) also contribute to the control of mycobacterial infections. They have been shown to accumulate in mycobacterial lesions, and to be able to secrete INF-γ, but recent data reveal that these cells are very important in monocyte recruitment into the granuloma, probably through the production of the chemokine macrophage chemoattractant protein 1 (MCP-1) (17).

Another important mechanism by which mycobacteria-infected macrophages can be lysed or activated by the immune system is through the CD1 molecule, a family of surface molecules with a high structural and conformational homology to major histocompatibility complex (MHC) class I molecules (59). Because of its high hydrophobicity and binding groove shape, CD1 has been shown to mediate specific T-cell recognition of non-peptide forms of mycobacterial cell wall constituents, such as mycolic acid lipids and lipoarabinomannan lipoglycans (LAMs) (75). CD1 proteins are expressed on antigen-presenting cells, broadly distributed in tissues and represent an important, complementary host effector mechanism to successful

mycobacterial elimination. One of the proposed mechanisms, by which mycobacteria can evade the immune system, is its protein antigen "sequestration" in the endosomes that can not be completely acidified and thus prevent antigenic protein escapement to compartments where they can associate with MHC class II (54). Conversely, glycolipids, such as LAM, efficiently escape from non-acidified endosomes, can be detected within a variety of compartments inside the macrophage and enter the CD1 antigen presentation pathway for immune recognition. Intact or fragmented mycobacteria are taken into macrophages via complement or Fcγ receptors, the mannose receptor or other mechanisms and transported to endosomes, where the mycobacteria has been shown to colocalize with CD1. CD1 proteins arrive in endosomal compartments either via cell surface recycling pathway or directly from the trans-golgi network. Once CD1 interacts with the mycobacterial antigen complexes and are displayed on the surface of antigen presenting cells, they can interact with the specific TCRs of CD1-restricted cells. Activated T cells can promote cytolisis of the infected cell and secrete cytokines including INF-γ. $CD4^-$ $CD8^-$ (Double Negative, DN) αβ T cells were the first reported CD1-restricted, antigen-specific T cells (58,1).

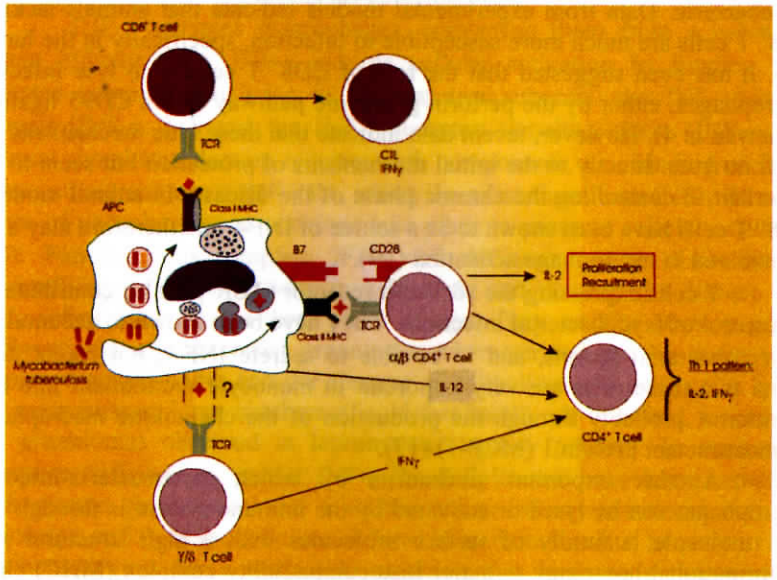


*Figure 1. Mycobacterium tuberculosis* is processed and presented by the macrophage to the $CD4^+$ T lymphocyte on the context of MHC class II. Macrophage secretion of IL-12 drives preferential activation of the type-1 pattern of immune response, with secretion of IFN-γ, crucial for activation of macrophage microbicidal mechanisms. The mycobacteria can also be presented on the context of MHC class I to the $CD8^+$ T lymphocyte, which can exert its cytotoxic function (CTL) against the infected macrophage. γδ T lymphocytes also participate in the immune response against *Mycobacterium tuberculosis* as an early source of IFN-γ.



However, more recent experiments have demonstrated that $CD8^+$ αβ T cells, DN γδ T cells, and possibly $NK1.1CD4^+$ cells can also respond to mycobacterial antigens presented on the surface of CD1 molecules.

## 3. Immunologic features of HIV-TB co-infection

The hallmark of AIDS is severe immunodepression caused by a gradual and progressive depletion of $CD4^+$ T lymphocytes. The $CD4^+$ T lymphocyte is the primary target for HIV infection and paradoxically, this is the pivotal cell in the cellular immune response, coordinating a number of very important immunologic functions. A loss of these functions results in progressive impairment of the immune response, leading to opportunistic infections and neoplastic diseases. In addition to a quantitative decline in $CD4^+$ T cells, a qualitative functional impairment is also observed (46, 25). Immunological abnormalities in T helper cell function may occur early in HIV infection before a significant decline in the $CD4^+$T cell numbers is observed (41,11).

$CD8^+$ cytotoxic T cells (CTLs) have also been implicated in the immune response against HIV. These T cells are shown to inhibit HIV replication in cell lines *in vitro*, either by cytolisis, or by the release of chemokines and other cytokines (68). In vivo, it has been demonstrated that there is an inverse correlation between plasma RNA viral load and the levels of circulating effective CTLs (47). Moreover, high levels of CTL activity have been correlated with slower rate of disease progression (55). However, the induction and persistence of HIV-specific CTL responses depend on continuous cognate helper function provided by the antigen-specific $CD4^+$ Th1 cells, which are destroyed or functionally impaired during the disease course. Additionally, because CTLs are highly activated during primary infection, due to high-level viremia, they can undergo deletion by clonal exhaustion. Other mechanisms used by the HIV to evade the CTL response include: 1)mutational epitope escape; 2) egress of CTLs from lymph nodes into the circulation during primary infection, where HIV replication is minimal; 3) trapping of HIV virions in Follicular Dendritic Cells (FDCs) of the lymphoid tissue, constituting a stable reservoir of infectious virions; 4) HIV sequestration in sites where CTL access is limited, such as infected glial cells in the brain; and 5) down-regulation of major histocompatibility complex (MHC) class I expression at the surface of the HIV-infected cell (reviewed in 56,38).

In addition to $CD4^+$ and $CD8^+$ HIV-specific T cells, antigen presenting cells, i.e., monocytes/macrophages and the dendritic cells, crucial cells in the generation of effective immune responses, can also have their function altered by HIV, either as a result of quantitative depletion by direct

cytopathogenicity or suboptimal formation of MHC-antigenic complexes (56).

In conclusion, it has been evident that the most important mechanism for the control of HIV and *M. tuberculosis* is a Th1 immune response, which is compromised in both infections. The most important type 1 cytokine, IFN-γ, was demonstrated to be drastically reduced in HIV/TB co-infected patients, while type-2 cytokine production is either maintained or increased (22). The lung is a central organ for both *M. tuberculosis* and HIV-induced pathophysiology. The $CD4^+$ resident lung cell population T lymphocytes, alveolar macrophages and fibroblasts are early infected by HIV, reducing the lung immune response which then becomes highly vulnerable to opportunistic infections, such as tuberculosis (40,19,39). Alveolar macrophages are crucial for effective early defense acting as antigen-presenting cells, secreting cytokines and recruiting T cells from the secondary lymphoid organs to the alveolar space. Although controversial, progression from HIV infection to AIDS has been demonstrated to be associated with a shift from the Th-1 to Th-2 cytokine pattern (10,9) Assuming that there is decreased Th-1 response at the time when HIV-positive individuals are infected by *M. tuberculosis*, or reactivate latent TB, Th-1 cells will secrete lower levels of INF-γ, compared to HIV-negative TB patients (71), contributing to the increased susceptibility to TB.

There is also evidence that *M. tuberculosis* may have the potential to enhance HIV replication. During the acute phase of active TB in HIV-infected patients, there is a substantial increase in RNA viral load (31). Because HIV replicates more efficiently in activated T cells, opportunistic pathogens such as *M. tuberculosis*, lead to production of cytokines, such as TNF-α and Il-1, which have been shown to enhance HIV-1 replication in monocyte cell lines in vitro (21,57,29). It has also been demonstrated that the mycobacteria enhances viral replication by inducing nuclear factor kappa-B (NFκB), the cellular factor that binds to promoter regions of HIV (74). A novel mechanism by which *M. tuberculosis* increases HIV replication has been recently suggested by Fraziano et al. (30). It was observed that CCR5 mRNA could be detected in cells from TB patients but not from controls and, in a series of *in vitro* experiments, CCR5 expression was also higher after TB infection than in non-infected control cells.

The challenges posed by the deadly alliance between HIV and *M. tuberculosis* are enormous. Prompt diagnosis and aggressive treatment of TB are crucial for improving survival in HIV-infected patients and the early identification of HIV-infection in TB patients promotes early introduction of anti-retroviral therapy, before deterioration of the immune system occurs.



RESUMO

Desafios enfrentados pelo sistema imune diante da co-infecção HIV-*Mycobacterium tuberculosis*

A Organização Mundial de Saúde (OMS) estima que um terço da população mundial esteja infectada por *Mycobacterium tuberculosis*, agente etiológico da tuberculose (TB). Cerca de 3 milhões de óbitos anuais ocorrem devido à TB, contabilizando isoladamente um número de mortes superior a qualquer outro agente infeccioso. Apesar da disponibilidade da vacina do Bacilo Calmette-Guérin (BCG) e da implementação da terapia supervisionada de curta duração (DOTS) em várias regiões do mundo, TB aparece como uma grave complicação da infecção pelo Vírus da Imunodeficiência Humana (HIV), tanto em países em desenvolvimento como em países industrializados. Os macrófagos representam as principais células efetoras na eliminação do bacilo e são infectados pelo *M. tuberculosis* por múltiplos mecanismos. Como um patógeno intracelular, a resposta imune protetora é mediada por células (CMI) e dependente da ativação do macrófago por citocinas do tipo 1, especialmente interferon-γ (IFN-γ). A produção de IFN-γ ocorre principalmente pelo linfócito T $CD4^+$ em resposta à interleucina-12, produzida pelo macrófago. Os linfócitos T citolíticos (CTLs) também desempenham papel importante na imunidade celular contra *M. tuberculosis*. A infecção pelo Vírus da Imunodeficiência Humana (HIV) é o maior fator de risco associado ao desenvolvimento de TB, aumentando as chances de infecção primária, reativação e reinfecção exógena. A gravidade da co-infecção decorre do fato de ambos os patógenos necessitarem de resposta imune do tipo Th-1, que se encontra comprometida nas duas infecções. Vários estudos têm demonstrado que TB acelera o curso da infecção por HIV. A replicação do HIV ocorre preferencialmente em linfócitos $TCD4^+$ ativados e a carga viral aumenta consideravelmente na presença de estímulos exógenos, como *M. tuberculosis*. O aumento da replicação viral ocorre devido às citocinas produzidas pelo macrófago ativado, especialmente fator de necrose tumoral-α e interleucina-1. Além disso, *M. tuberculosis* induz produção de fator nuclear kappa-B, que se liga a regiões promotoras do HIV, aumentando sua replicação. O diagnóstico precoce da co-infecção HIV/TB é de extrema importância para a introdução imediata dos regimes terapêuticos tuberculostáticos e anti-retrovirais, em fase mais precoce da imunodeficiência, aumentando assim a sobrevida do paciente.

UNITERMOS: HIV/aids. *Mycobacterium tuberculosis*. HIV/TB co-infecção. Resposta imune.

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