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Tuberculosis and HIV – Doubling the Fatality

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Abstract

Tuberculosis (TB) and HIV/AIDS infection are one of the most ubiquitous and deadliest communicable diseases in the world. They cause millions of deaths each year and are recognized as major threats for public health worldwide. The corresponding pathogens (*Mycobacterium tuberculosis* and HIV) share overlapping epidemiology – they affect low-income countries and place an immense burden on their feeble health care systems. Over the last decades, the natural history of both diseases has changed; in addition to devastating single HIV and TB infections, the coinfection with both pathogens has emerged and has spread in pandemic scale. When present as dual infection in an individual, *Mycobacterium tuberculosis* and HIV potentiate each other and kill in cooperation the host. TB is the leading cause of death in HIV-positive patients and in turn HIV infection is the strongest risk factor for the development of new or reactivation of dormant TB disease. Both pathogens (as single or dual infection) provoke a robust immune response in the infected host but the immune system does not achieve to eliminate the infectious agent(s). The failure of immune defense results in vulnerable immune balance between the micro- and the macroorganism and often ends up in a fatal outcome.

Keywords: Tuberculosis, HIV, immunity, co-infection

1. Introduction

Human immunodeficiency virus (HIV) and tuberculosis (TB) represent, respectively, the first and the second leading cause of death from infectious disease in the world. Both are responsible for approximately 3 million deaths annually [1].

Either HIV or TB, when present as a single infection, irreversibly affects and exhausts the immune system of the infected person. Moreover, if they simultaneously coexist in an

individual (coinfection), they act in synergy to deteriorate the defense mechanisms of the host's immunity and to accelerate the fatal scenario.

In this chapter, we will review current knowledge of innate and adaptive immune responses against TB and HIV infections. We will discuss in detail the immunological basis behind the dual threat of TB/HIV coinfection.

2. Epidemiology

2.1. Epidemiology of HIV pandemic

HIV infection is a viral disease that affects host immune system and makes the host strongly susceptible to opportunistic infections. It spreads among human population via sexual contact, sharing needles during drug injection, transfusion of contaminated blood products, or during births from HIV-infected women.

Since the late 20th century, HIV infection has become a global pandemic and a major challenge for public health authorities at the national and international levels. At the end of 2013, 35 million people were living with HIV worldwide [2]. During the same year, approximately 2.1 million people were newly infected with HIV. Sub-Saharan Africa is the most affected region in the world—almost 70% of the prevalent and the new HIV-positive cases are diagnosed there. The socio-economic status of the countries in the core of HIV pandemic determines the low number of infected people currently on adequate antiretroviral therapy (only 36% of overall cases).

2.2. Epidemiology of tuberculosis

Tuberculosis (TB) is an infectious disease caused by bacterial species grouped in *Mycobacterium tuberculosis* complex—MBTC (*M. bovis*, *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M. pinnipedii*). Among these mycobacterial species, the most important and major cause of human tuberculosis is *Mycobacterium tuberculosis*. It is a widespread microorganism that readily colonizes and infects humans. Primary infection represents clinical manifestation in only 10% of infected individuals, while in the remaining 90%, *M. tuberculosis* stays in latent form without showing any obvious clinical signs—latent (dormant) tuberculosis [3].

The World Health Organization (WHO) recognizes TB as “a global public health emergency” and “one of the world's deadliest communicable diseases” [1]. At least one-third of the world population (approx. 2 billion people) is currently infected with latent mycobacteria and has a risk, although low (5–10%), to develop an active disease during the life course [1]. In 2013, 9 million new TB cases occurred worldwide (TB incidence: 126 cases per 100,000 population) and the prevalent cases were 11 million (TB prevalence: 159 cases per 100,000 population). Despite the efforts at the international, national, and regional level and the significant progress in the detection and management of TB infection, still the incidence, prevalence, and mortality rate of TB are unacceptably high.

2.3. Epidemiology of TB/HIV coinfection

People living with HIV have 26–31 times higher risk to develop active TB than the normal population [1]. Both diseases are epidemiologically and biologically connected—TB is the leading cause of death in HIV-positive patients and in turn HIV infection exacerbates the gravity of TB. Due to the global circulation of HIV, the incidence of TB — an infection previously thought to be almost eliminated at least in developed countries — is still high in both developing and high-income countries. HIV disrupts the host immune system through significant depletion of CD4+ lymphocytes, a mechanism that readily facilitates the reactivation of latent TB to an active disease. Therefore, HIV is the strongest risk factor for the development of new or the reactivation of dormant TB disease, including multidrug-resistant TB, an infection resistant to at least two of the first choice drugs for TB treatment, isoniazid and rifampicin. HIV infection predisposes TB-infected patients to antibiotic (rifampicin) resistance through gastrointestinal malabsorption of TB medications [4]. On the other hand, *M. tuberculosis* enhances HIV replication [5] and decreases the CD4+ T cell counts in HIV-positive patients [6].

As one-third of the total world population is currently infected with latent *M. tuberculosis* [1] and almost 1% of the adult population is living with HIV, it is not surprising that 1.1 million (13%) of the 9 million people who developed TB in 2013 were at the same time HIV-positive and 360,000 of the overall 1.5 million TB deaths for 2013 were HIV-positive. Most of them (78%) were living in low-income economies in Sub-Saharan Africa, a region where 50–80% of TB patients have HIV coinfection[1].

WHO recommends regular screening of TB for all people living with HIV at every visit to a health care specialist [7]. WHO also recommends that routine HIV testing should be offered to all patients with presumptive and diagnosed TB, as well as to partners of known HIV-positive TB patients.

In addition to the increase in TB incidence, the worldwide HIV pandemic changed the average age of TB-infected people. In contrast to normal populations where TB is most prevalent among elderly people, in regions with significant number of HIV-positive cases, the most affected age by TB is the reproductive age (20–45 years). This leads to the consecutive increase in the number of TB-infected children [8].

3. Immunology of tuberculosis

3.1. The first date

Primary infection with *M. tuberculosis* occurs after inhalation of aerosolized infectious nuclei containing mycobacterial cells [9]. Any person with active TB can transmit the pathogen through coughing or sneezing, infecting 2–10 healthy individuals. Tubercle bacilli survive in the air for a short time (few hours), but the infective dose is relatively low (only 1–10 living cells). Infectious nuclei bigger than 10 µm gravitate in the nasal conchae and the nasopharynx. Those measuring between 5 and 10 µm enter the lower respiratory tract and mucociliary

escalator eliminates them. Only infectious droplets smaller than 5 μm persist in the distal lung alveoli and can cause infection.

In most cases, the non-immune mechanisms do not allow the development of the infectious process. If infection occurs, the immune system in the lungs activates the first-line innate defense and then, several weeks later, an adaptive anti-mycobacterial immune response is activated. The strong immune response against *M. tuberculosis* works in two warring interests — on one hand, it restricts *M. tuberculosis* dissemination outside the initial infection place, and on the other hand, it supports its survival and silent presence for years in healthy individuals. The human immune system succeeds to completely eliminate *M. tuberculosis* in only 10% of infected cases, while in the remaining 90%, it fulfills in different degrees and controls the infection by turning it into the latent state [3].

3.2. Innate immunity

The early stages of TB infection consist of inhalation of tubercle bacilli and initial encounter between the immune system and the pathogen. Alveolar macrophages and sometimes nonprofessional phagocytic cells (alveolar epithelial cells) are the first to recognize *M. tuberculosis* cells [10, 11, 12]. Still, unknown intrinsic virulent features of *M. tuberculosis* strains and individual host immune differences are crucial for the fate of tubercle bacilli in the early days of infection. The most favorable outcome is the definitive destruction of *M. tuberculosis* by non-specific defense mechanisms in the macrophages. In this case, adaptive immunity does not develop and participate in the protection.

If bacteria survive bactericidal macrophage action, they can multiply intracellularly to destroy the infected macrophage and to release attractants for monocyte and dendritic cells accumulation. The attracted monocytes will differentiate into macrophages that in turn can recognize new *M. tuberculosis* cells to increase the population size of infected cells in the lung and sometimes in extra pulmonary locations. All these immune cells readily engulf *M. tuberculosis* cells but are unable to completely destroy them. Thus, the number of *M. tuberculosis* in the place of infection progressively increases.

Macrophages and dendritic cells bind *M. tuberculosis* cells via different receptors: toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD-) like receptors (NLRs), mannose receptors (CD207), dendritic cell-specific intercellular adhesion molecule grabbing nonintegrins (DC-SIGN), Dectin-1 receptors, complement receptors, and others [3]. Among TLRs, the most important for pulmonary TB cases are TLR2, TLR4, and TLR9 [10–12]. TLR2 recognizes tubercle polysaccharides and via binding with TLR1 can identify tubercle cell wall 19 and 27 kDa lipoproteins—important *M. tuberculosis* cell surface ligands. Furthermore, bacterial DNA released after bacterial destruction in lysosomes activates TLR9.

The interaction between *M. tuberculosis* and TLRs induces a signal proinflammatory cascade and provokes secretion of cellular signals—TNF-alpha, IL-1, IL-6, IL-12, IL-18, IL-15, IL-23, IFN-gamma, and chemokines. The infected macrophages also release small molecules—chemokines CCL, CCL3, CCL4, CCL5 (8–10 κDa)—to attract other blood monocytes and neutrophils [13], which after differentiation can directly display bactericidal action towards

M. tuberculosis. Interleukins and chemokines serve both to attract other immune cells (lymphocytes) and to activate them.

3.3. Cell-mediated immunity

A fundamental characteristic of *M. tuberculosis* infection is the considerable delay in the onset of adaptive immunity, achieved by efficient control and management of the innate immunity; the host establishes an effective cell-mediated immune response several weeks (2–8) after the initial infection [3]. Nonetheless, the initiation of cell-mediated adaptive immunity, though delayed, is crucial for efficient control of further TB invasion.

The matured dendritic cells move to the regional lymph nodes where they initiate specific cell immune response by presenting the ingested mycobacterial antigens to the naïve T cells. Dendritic cells are a primary target for *M. tuberculosis* after aerosolic lung infection [14, 15]. They are professional antigen presenting cells (more effective than macrophages) and strong T cell activators. One of the mechanisms used by *M. tuberculosis* to delay the cell-mediated immunity is the efficient postponement of the movement of dendritic cells towards regional lymph nodes. In the lymph nodes, infected dendritic cells produce IL-12 [16] for the activation of NK cells and stimulation of INF-gamma release from T-lymphocytes [17]. Antigen presenting dendritic cells prompts T cells to differentiate and to migrate, under the navigation of secreted adhesion molecules and chemokines, to the initial site of infection.

The concentration of macrophages, T-lymphocytes, dendritic cells, and other immune and lung cells (epithelial, giant multinuclear Langerhans' cells, plasma cells, neutrophils, fibroblasts) in the place of infection is known as granuloma. The process of granuloma formation limits the spread of *M. tuberculosis* to other organs and restricts tissue's damage by separating the infected place [18]. But at the same time, granuloma microenvironment ensures the needed conditions for mycobacterial growth and multiplication.

Both human and animal granulomas contain giant multinuclear Langerhans' cells produced after the fusion of macrophages [18, 19]. In these cells, tubercle bacilli cannot multiply and survive successfully.

Neutrophils are important for early control of acute bacterial infection [20] as they immediately migrate to the place of mycobacterial infection and start bacterial phagocytosis [21]. Infected neutrophils produce IL-8 and TNF for activation of alveolar macrophages and limitation of the infection [22].

Both CD4+ and CD8+[23] contribute to the stimulation of macrophages and lysis of chronically infected macrophages (via INF-gamma action). The principal role in cell-mediated immunity against tuberculosis is played by CD4+ T-lymphocytes. CD4+ express *a/b* T cell receptors to recognize mycobacterial antigens on the surface of antigen-presenting cells such as monocytes, macrophages, or dendritic cells [24]. Then, CD4+ lymphocytes efficiently induce apoptosis of macrophages [25] and stimulate the cytotoxic function of CD8+ [26].

CD8+ cells play an important role in IFN-gamma release, cell lysis and bacterial killing [27]. Some CD8+ lymphocytes may also recognize surface antigens presented by Class I MHC

molecules—MHC class I-restricted cytotoxic T-lymphocytes (CTL). They are able to eliminate infected macrophages and also to kill intracellular bacteria via production of granulysin (a cytolytic and proinflammatory substance) [28].

Other immune cells—CD1 restricted T cells, γ/δ -T cells, and cytotoxic T-cells—also protect lung tissue against tuberculosis. T cells of type γ/δ are the first line of defense against microbial antigens and the connection between innate and adaptive immune response [29]. They have cytotoxic activity and may present mycobacterial antigens to CD8+ and CD4+ lymphocytes. In response to IL-23 secreted from infected dendritic cells, the γ/δ -T cells start to release IL-17 for accumulation of additional immune cells in the place of infection.

Activated macrophages represent higher phagocytic activity against extracellular mycobacteria. On the base of T-lymphocyte stimulation, two types of macrophages are known: classically activated macrophages (CAM) and alternatively activated macrophages (AAM). During the immune response against tubercle bacilli, activation of macrophages by T-lymphocytes is achieved mainly through release of IFN-gamma and other Th-1 cytokines. The Th-1 cytokines (INF-gamma, TNF-alpha, IL-1beta) induce CAM to kill tubercle bacilli via production of nitric oxide synthetase (iNOS). This enzyme catalyzes synthesis of nitric oxide (NO), a powerful antimicrobial substance. The Th-2 cytokines (IL-4 and IL-13) activate AAM to produce anti-inflammatory cytokines and arginase. They both compete for arginine utilization with iNOS [30]. The increased arginase activity stimulates tissue repair but at the same time restricts bacterial killing [31].

M. tuberculosis (particularly the virulent strains and not the attenuated ones) can survive in phagosomes of macrophages by suppressing the fusion between formed mycobacterial phagosome and lysosomes [32]. Other mechanisms to overcome bactericidal activity of macrophages include the prevention of phagosomal acidification and guidance of infected cells towards necrosis. Necrosis is a form of cellular death characterized by plasma and mitochondrial membrane disruption. In this way, tubercle bacilli leave infected macrophages and spread to other cells. Moreover, *M. tuberculosis* may inhibit the programmed cell death or apoptosis, a cellular death that protects further bacterial spread by preserving the cellular integrity of infected macrophage. Apoptotic macrophages transmit mycobacterial antigens to dendritic cells and induce more efficient T cell response.

3.4. Humoral immunity

In addition to cell-mediated immunity, humoral immune response plays a major role in TB infection control. The formed antibodies cannot transfer immunity but have an opsoning role and facilitate the phagocytosis by the macrophages and the cytotoxic function of T-lymphocytes [33]. Besides their antibody synthetic function [34], B-lymphocytes can present mycobacterial antigens to T cells [35]. They stimulate proliferation and differentiation of T-lymphocytes by the production of different cytokines. Specific effector B1-cells secrete Th1-cytokines—IFN-gamma and IL-12—while B2-cells secrete IL-4, typical for Th2-cells. Furthermore, activated B cells can produce IL-6 for T cell stimulation and IL-10 for inhibition of dendritic cells and macrophages.

3.5. Latent tuberculosis

The late stage of TB infection represents a prolonged (in many cases lifelong) suppression of mycobacterial cells as a result of the dynamic balance between the pathogen and the host immunity. *M. tuberculosis* persists within the granulomas and escapes total disruption by the immune system. In latent TB, the host and tubercle bacilli coexist in “perfect” synergy; the granuloma represents a place for bacterial survival and place for host attack [36]. Usually, the host immune system succeeds to manage the infectious process, but in extreme conditions (starving, diabetes, alcohol abuse, corticosteroid treatment, and especially supplementary HIV infection) the disease can progress. This progression is linked to granuloma disruption and further dissemination of *M. tuberculosis*. The late tuberculosis occurs in the presence of sensitized T-lymphocytes and already existing specific defense mechanisms. This determines rapid limitation of the process with strong caseous necrosis, cavern formation, and fibrosis.

4. Immunology of HIV

4.1. Entry through the mucosal barrier

The principal route of HIV entry into the human body is through the mucosal epithelial surfaces (mainly genital or rectal). The virus prefers to infect immune cells expressing CD4+ receptors on their surface—CD4+ helper T cells, macrophages, and dendritic cells—all present in activated state in the mucosal lymphoid tissues.

HIV crosses the intact epithelial layers via interaction with dendritic cells and/or CD4+ helper T cells. The CD4+ receptor of these cells recognizes the viral envelope glycoprotein 120 (gp120) and causes its conformational change. This makes possible the binding with one of the auxiliary co-receptors: CCR5 or CXCR4. The second binding allows viral glycoprotein 41 (gp41) to integrate within the cell membrane and viral genome to access the host cytoplasm.

After entry into the cell, viral RNA—under the action of reverse transcriptase and integrase—turns into double-strand DNA and integrates into the host DNA. The integrated copy of HIV nucleic acid (named provirus) can stay in latent form for years and can become active at any time to complete the viral life cycle and produce new virions.

The principal target for HIV is the activated CD4+ T-lymphocyte expressing CCR5 or CXCR4 co-receptor. The high number of CD4+ T cells (especially memory CD4+CCR5+ T-lymphocytes) in the mucosa is ideal for HIV replication [37]. In contrast, mucosal dendritic cells do not express CD4+ or CCR5 receptors [38] but they do express other receptors that successfully recognize HIV envelope proteins—dendritic cell-specific intercellular adhesion molecule grabbing nonintegrins (DC-SIGN) and langerin [39].

4.2. HIV expansion

Early after the entry of HIV, the primary infected T-lymphocytes attract and activate other immune cells to expand the initial place of infection. The infected local site starts to grow until

the detachment of the infected cells. Thus, the virus disseminates from the mucosal surfaces to the regional lymph nodes (usually in 10 days after the infection) and then throughout the body. The virus can be detected in all lymphoid organs but the highest number of viral particles concentrates in the mucosal lymphoid tissues (such as gastro-intestinal associated lymphoid tissue). Dendritic cells in lymph nodes and mucosal lymphoid tissues present the HIV antigens to naïve B cells and T cells, prompting them to differentiate and activate. In these first stages, the viral load is significant and CD4⁺ T cells count starts to decline rapidly.

In many cases, the early events of viral expansion (acute stage) are not clinically manifested. In some people, influenza-like or mononucleosis-like symptoms may occur several weeks after the exposure to infection but they are not specific and often misdiagnosed.

4.3. T cell-mediated immune response during HIV latency

Several months after the initial infection, a precise balance between the virus and the immune response (both cell-mediated and humoral) is established. Host immune system (especially CD8⁺ lymphocytes) succeeds to control viral replication at some degree but the elimination of target CD4⁺ population continues. This represents the chronic (latent) phase in HIV infection, clinically manifested with decreased viral load and appearance of specific anti-HIV antibodies in the blood of infected individuals.

Although the major characteristic of HIV infection is the depletion of CD4⁺ T cells, other lymphocyte types are also affected. HIV notably influences naïve T cells (both CD4 T naïve cells and CD8 T naïve cells) during the asymptomatic phase of the infection [40]. Any T cell-mediated immune response requires new naïve T cells and their depletion results in progressively compromised immunity. The reduction in naïve T cell counts is probably due to decreased thymic output and increased T cell turnover in HIV-positive patients [41]. Furthermore, during HIV asymptomatic phase, the overall CD8⁺ count remains the same as before infection but significant alteration in the ratio memory/naïve CD8⁺ cells occurs, the normal predominance of naïve CD8⁺ is replaced by the domination of memory cells (in many patients, the compartment of CD8⁺ memory cells represents more than 80% of all CD8⁺ circulating cells) [40].

The cellular immune response mediated by CD8⁺ cytotoxic T-lymphocytes (CTLs) plays a crucial role in HIV infection [42]. The precursor CTLs recognize viral antigens expressed on the surface of presenting cells. They become active with the help of IL-2, IFN-gamma, and TNF-alpha (produced from CD4⁺ T cells) and can directly eliminate infected CD4⁺ lymphocytes via secretion of perforin (a cytolytic protein) and granzymes (serine proteases). The increased ability to secrete perforin is specific for CD8⁺ T cells from small group HIV-positive individuals who maintain HIV replication in undetectable levels (elite controllers) [43] and who do not progress immunologically towards AIDS in the absence of antiretroviral treatment.

Simultaneously with the host response, the virus starts a mutation process to escape CD8⁺ recognition by changing epitopes and to correct the present viral variant. At this moment, a balance between host elimination and replication of new HIV variants is established. However,

CD8+ immune response, as well as humoral response, strongly needs CD4+ T helpers and gradually with CD4+ depletion, the CD8+ control fails to maintain the viremia.

The loss of effective antiviral response leads to a constant stimulation and repeated activation of HIV specific CD8+ T cells. This chronic activation soon exhausts the pool of CD8+ lymphocytes together with CD4+ T cell one.

The elevated activation is characteristic not only for CD8+ and CD4+ T cells, but also for B cells, NK cells, and monocytes. In HIV-seropositive patients, even in early stages of infection, high levels of proinflammatory cytokines (TNF-alpha, IL-6 and IL-1 β) and chemokines (MIP-1alpha, MIP-1beta and RANTES) are detected [37].

The HIV life cycle is closely related to the extent of immune system activation. Activation of the immune cells enhances the entry of HIV into the cytoplasm because the auxiliary coreceptors are upregulated under immune stimulation [44]. It also increases the level of provirus transcription together with the normal cellular transcription [45]. The exhausted CD8+ T cells diminish secretion of immune-stimulatory cytokines, slow down proliferation and suspend killing of infected cells [46]. HIV infection stimulates upregulation of CD8+ inhibitory receptors (Programmed Death-1 (PD-1), T cell immunoglobulin, and mucin-domain-containing molecule-3 (Tim-3) [47,48]) that downregulate CD8+ immune response and maintain T cell tolerance.

4.4. Humoral immune response against HIV

The humoral immune response against HIV is mediated by specific anti-HIV antibodies produced from B-lymphocytes several weeks to several months after the initial infection. HIV cannot replicate into B-lymphocytes but influences their activation and apoptosis. Unmatured B-lymphocytes differentiate under the action of Th1 cytokines (IL-4, IL-5, IL-6, IL-10, TGF-beta) into plasma cells producing large amounts of binding and virus-neutralizing antibodies. Antibodies target free viral particles in the HIV-positive blood and a small quantity of them can also eliminate infected cells.

HIV specific antibodies recognize viral envelope (envelope proteins gp120 and gp41) and protect host cells from viral entry, but the virus successfully escapes the antibodies' binding via continual mutations. Memory B cells constantly produce new variants of antibodies and soon become exhausted.

4.5. AIDS

The latent phase can last several years (usually up to ten) and terminates finally with the development of AIDS and death. In the final stage, HIV infection completely exhausts the host immune system and especially the CD4+ T cell pool. AIDS is immunologically diagnosed by a CD4+ count less than 200 per μ L or/and clinically by the occurrence of opportunistic HIV-related diseases.

5. Immunology of TB/HIV coinfection

5.1. HIV impact on TB infection

TB is the leading opportunistic infection and major cause of death in HIV-seropositive people. There is some evidence that both HIV-negative and HIV-positive persons have the same chance to be infected with TB [49]. In contrast, other studies have found that already existing HIV infection increased the risk of newly acquired TB [50, 51] and relapse of dormant *M. tuberculosis* [52]. However, there is unanimity that HIV exacerbates TB progress and accelerates the fatal end in coinfecting individuals.

Existing data outlines two main hypotheses how HIV influences the course of TB infection: 1. HIV manipulates bactericidal activity of macrophages against *M. tuberculosis*; and 2. HIV kills CD4⁺ T cells within granulomas and facilitates *M. tuberculosis* survival and dissemination.

HIV impairs macrophages in HIV-positive patients turning them more susceptible to *M. tuberculosis* invasion [53]. First, HIV upregulates some of *M. tuberculosis* receptors on macrophages to favor tubercle bacilli entering into the cell [54]. Second, HIV modulates oxidative stress-dependent bactericidal activity in monocytes by diminishing their capacity to produce ROS [55]. As a result of increased levels of IL-10 (an anti-inflammatory interleukin) and decreased TNF- α production, infected macrophages escape apoptosis [53, 56]. Thus, more macrophages are directed towards necrosis, a mechanism that increases the *M. tuberculosis* survival and dissemination in the lungs and other extra pulmonary locations. Furthermore, HIV alters the acidification of phagosomes in *M. tuberculosis*-infected macrophages [57], changing the rate of tubercle bacilli elimination.

HIV manifests its presence by gradual depletion of CD4⁺ T cells, a main feature of HIV infection and clinical sign for progression towards AIDS. The low CD4⁺ cell count makes the host more susceptible to tubercle bacilli as the immune system cannot establish an efficient cell-mediated immune response. The risk of reactivation of latent TB, acquirement of new TB infection, and/or of dissemination of TB towards extra pulmonary locations increases with the decrease of CD4⁺ cell count; patients with CD4⁺ counts >350 cells/ μ L have unaltered clinical and radiographic presentation as HIV seronegative patients, while patients with CD4⁺ counts <350 cells/ μ L have atypical chest X-ray findings and frequent extra pulmonary TB. HIV-positive patients in South Africa with CD4⁺ counts <200 cells/ μ L are more susceptible to *M. tuberculosis* infection than HIV-positive individuals with CD4⁺ counts >500 cells/ μ L regardless of antiretroviral therapy applied [58].

The insufficient CD4⁺ T number fails to control granuloma formation and maintenance, therefore leading to higher incidence of extra pulmonary TB and enlarged risk of reactivation of latent infection in HIV-positive patients. Caseous necrotic granulomas—typical for single TB infection—are rare in TB/HIV coinfecting patients. Despite the same number of granulomas and acid-fast stained bacilli in TB infected and TB/HIV coinfecting persons [59], granulomas from dual-infected individuals are easily disrupted and infection can readily disseminate into multiple organs to form diffuse lesions [60].

However, HIV influence on TB course may only partially depend on CD4⁺ depletion, as HIV-positive miners in South Africa had an increased risk (2 to 3 times higher) of developing active TB in the first and second year after HIV seroconversion, when the number of CD4⁺ T-cell was still high [61]. HIV-positive individuals with preserved CD4⁺ T cell counts (during an antiretroviral treatment) also have an increased risk of developing TB infection. This suggests that additional immunological changes could happen during HIV infection, making the host more susceptible to TB. Such possible mechanism is the observed uniform distribution of CD8⁺ T cells within the granuloma, in contrast to the peripheral findings in the single TB infection [62]. HIV also specifically diminishes production of IFN-gamma, IL-2, and IL-12 [63], and suppresses proliferation of TB-specific T cells. Several months after HIV seroconversion, the number of *M. tuberculosis* specific CD4⁺ memory cells decreases significantly [64].

5.2. TB importance in HIV infection

HIV recognizes immune cells expressing CD4⁺ glycoprotein on their surface: CD4⁺ T-cells, macrophages, and dendritic cells. All of these cellular types are involved in TB pathogenesis and immune response. HIV also needs activated immune cells for replication and propagation; such cells are abundantly present during *M. tuberculosis* primary or latent infection. In this way, it can be speculated that TB infection areas (granulomas) create the optimal environment for HIV propagation.

HIV-positive patients who developed TB have an increased viral load during the acute phase of TB disease [65, 66]. Lung tissue samples from patients with TB have increased HIV viral load when compared to HIV-positive patients without lung disease or plasma samples from the same TB patients [67]. This suggests that a TB-infected lung has elevated local HIV replication in vivo. In addition, HIV replication is activated in TB-infected alveolar macrophages [68], lymphocytes, and CD14⁺ macrophages of the pleural space [69].

Infection with *M. tuberculosis* also enhances the level of inflammatory cytokines and chemokines. Their release stimulates HIV replication and increases viral load. Pleural fluids from patients with active TB provoke HIV replication in vitro via production of TNF-alpha, IL-6, and IFN-gamma [70].

Coinfected individuals have increased incidence and death rate of HIV-related opportunistic infections comparing to HIV-positive but TB-negative patients with the same level of immunosuppression (absolute CD4⁺ count) [71], indicating that *M. tuberculosis* accelerates the clinical course and outcome of HIV infection.

6. Concluding remarks

TB/HIV coinfection represents a leading threat to public health worldwide. Despite the extreme research effort, many aspects of the exceptionally complicated immunology of concurrent TB and HIV infections still need to be elucidated. Diagnosis of HIV/TB coinfection is challenging as both infections have overlapping clinical manifestations, which often lead to

late or misdiagnosis. Furthermore, TB and HIV as well the coinfection mostly affect poor and developing regions where competent health care is hardly accessible.

Changes in both innate and adaptive immune response demand well-organized clinical and laboratory studies to understand possible mechanisms by which HIV and TB disrupt in perfect and fatal cooperation the immune system of the host.

Abbreviations

AAM – Alternatively activated macrophages

AIDS – Acquired immune deficiency syndrome

CAM – Classically activated macrophages

CCL – CC chemokine ligand

CTL – Cytotoxic T-lymphocytes

DC-SIGN – Dendritic cell-specific intercellular adhesion molecule grabbing nonintegrins

HIV – Human immunodeficiency virus

IFN – Interferon

IL – Interleukin

iNOS – Nitric oxide synthetase

MBTC – *Mycobacterium tuberculosis* complex

MHC – Major histocompatibility complex

MIP – Macrophage inflammatory protein

NK – Natural killer cells

NLR – NOD-like receptors

NO – Nitric oxide

NOD – Nucleotide-binding oligomerization domain

PD-1 – Programmed death-1

RANTES – Regulated on activation, normal T cell expressed and secreted

ROS – Reactive oxygen species

TB – Tuberculosis

TGF – Transforming growth factor

Tim-3 – T cell immunoglobulin and mucin-domain-containing molecule

TLRs – Toll-like receptors

TNF – Tumor necrosis factor

WHO – World Health Organization

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