Interaction between the Human Immunodeficiency Virus (HIV) and *Mycobacterium tuberculosis* (MTB): HIV-1 induced CD4 T cell depletion and the development of active Tuberculosis

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Abstract

Purpose of review: HIV infection is the main driver of the HIV/TB syndemic in southern Africa since the early 1990s, when HIV infection rates started to increase exponentially and TB incidence rates quadruplet simultaneously. Here we discuss pathogenic mechanisms of HIV induced CD4 T cell depletion and their potential impact on immune control of Mycobacterium tuberculosis.

Recent findings: Depletion of Effector Memory (EM) CD4 T cells from the air-tissue interphase, their dysfunctional regeneration and the preferential depletion of MTB-specific CD4 T cells from circulation and from the air-tissue interphase might be key factors for the increased susceptibility to develop active TB after HIV infection.

Summary: Early initiation of antiretroviral therapy or the development of an efficacious HIV vaccine would be the best options to reduce morbidity and mortality associated with the HIV/TB syndemic.

Keywords: HIV, Tuberculosis, CD4 T cell

Introduction

Originating from multiple zoonotic transmissions of simian immunodeficiency virus (SIV) to humans in west and central Africa, Human Immunodeficiency Virus 1 (HIV) started to spread in the early 1900s into larger populations. The most successful branch of HIV, group M was transmitted from the chimpanzee *Pan troglodytes troglodytes* in which it is endemic [1]. Initially the spread of HIV-1 group M was geographically confined to western-central Africa, but international migration and travel enabled a successful spread across the world in the second half of the twentieth century. Since its discovery as the causative agent of the Acquired Immunodeficiency Syndrome (AIDS) in 1983 [2-3], HIV prevalence rates have increased steadily on a global scale to 33 Million infected subjects - 0.8% of the adult population - in 2009 [4]. The most dramatic increase in HIV prevalence rates was observed in sub-saharan African countries and an estimated 68% of globally HIV infected people live in Sub-Saharan Africa. Particularly South African countries are at the “epicenter” of the HIV epidemic - with adult prevalence rates of up to 25% population[4].

Globally, active tuberculosis (TB) remains among the leading causes of death from an infectious agent. In 2010, the estimated global TB incidence rate was 128 cases per 100,000 population, which equates to 8.8 million (range, 8.5–9.2 million) incident TB cases [5]. Since the 1990s the world wide TB incidences have developed quite divergently. While in most parts of the world TB incidence rates remained stable or declined, African incidence rates increased by almost 30%. This increase was most pronounced in Southern Africa, especially South Africa where the incidence nearly quadrupled to 981 cases per 100,000 population (95% uncertainty interval 806-1170). HIV/TB co-infection numbers (figure 1; red line) indicate that in these countries a large proportion of the TB incidence is related to immunodeficiency caused by HIV infection. In South Africa approximately 60% of TB incident cases are HIV infected and in total the African Region accounts for 82% of TB cases among people living

with HIV [5]. The dramatic mortality of this co-epidemic in Southern Africa is highlighted by a recent post mortem-study of young inpatients (18-45years) of a hospital in KwaZulu-Natal that found that 94% were HIV+ and 69% of them had active TB or were currently on TB treatment at the time of death [6].

The HIV related factors that contribute to the increased prevalence of active TB in HIV high-endemic areas are obvious. An impaired immune system will change the acquisition rate of infection following exposure. Similarly will the loss of immune control influence the rate of recurrence of sub clinically infected individuals. The proportional contribution of these factors is unclear and subject of an ongoing debate [7]. There are data from cohorts that indicate a 2-3 fold increase of active TB disease within the first year after HIV seroconversion and that is not a direct function of the depletion of the blood CD4 cells [8-9]. In a macaque model for HIV induced TB reactivation, 8 of 8 macaques, who were latently infected with MTB, reactivated within less than a year after infection with a high dose of Simian Immunodeficiency Virus (SIV) [10].

Here discuss how the depletion of memory CD4 T cells and MTB-specific CD4 T cells after HIV infection could contribute to loss of MTB immune control.

Immunity to *Mycobacterium tuberculosis* infection

Infection with MTB is caused by aerosolic transmission and primarily targets the respiratory system. Immune correlates of protection are best defined in the murine model. Although not reflecting all aspects of human TB pathogenesis, it serves as a good animal model to elucidate fundamental questions of host-pathogen interaction and immunity [11-12]; upon inhalation, MTB is phagocytosed by alveolar macrophages and myeloid Dendritic cells (mDCs) [13]. MTB is adapted to survive and replicate intracellularly within the macrophage phagosome.

MTB infected myeloid Dendritic cells (DCs), which actively sample the mucosal environment, migrate to the draining lymph nodes to support initiation of the MTB-specific adaptive immune responses [13-14]; a delay in priming the adaptive immune response is thought to be critical in establishing bacterial persistence [14-15]. Initial priming of the adaptive immune response triggers expansion and phenotypic and functional maturation of MTB-specific T cells, which recirculate and home to the primary site of infection, where they activate infected macrophages through the secretion of Interferon gamma (IFN- γ) and Tumor Necrosis Factor alpha (TNF) [16-17]. These Th1 cytokines are important mediators for arresting intraendosomal MTB growth, for microbial killing and, perhaps most importantly, for granuloma formation and maturation [12,18]. In addition, IFN- γ /TNF independent T cell mediated effector mechanisms also contribute to the control of MTB [16,19]. The TB granuloma is the hallmark of the MTB-specific immune response and locally restricts mycobacterial spread both in humans and in mice [12,20]. Murine studies using advanced dynamic imaging methodology, have shown a surprisingly mobile CD4 T cell population during early granuloma formation and only low frequencies of IFN- γ secreting mycobacteria-specific CD4 T cells (5-8%) at a given time point [16,21]. Indeed, during these early stages of granuloma formation, the T cells surrounding the mycobacteria are somehow reminiscent of riot police kettling tactics to contain street protests.

MTB-specific CD4 T cell responses play a central role in the control of aerosolic MTB infection [15,17,22-23]; Antibody-mediated depletion of CD4 T cells but not CD8 T cells, slightly reminiscent of HIV pathogenesis, drastically reduces control of MTB growth and survival upon challenge of mice [24]. Perhaps most conclusive, adoptive transfer of transgenic MTB-specific CD4 T helper 1 cells potently restricts MTB growth in the lungs of recipient mice in a dose dependent manner [17]. Thus, although CD4 T cell independent

mechanisms are likely to contribute to microbial immunity, CD4 T cells are key in the control of murine MTB infection.

Protective immunity against human TB remains poorly characterized. Human genetic mutations in IL-12p40 or IFN- γ receptor genes [25] or treatment with TNF antagonists [26] are associated with a greater risk of TB disease progression, consistent with a central role of “TH1 cytokines” for efficient control of MTB infection also in humans. None-human primate experiments support an important role for CD4 T cells [10,27], but also suggest a more prominent role for CD8 T cells, which include none-classical CD8 T cells found in humans, but not in mice [28]. Thus, impaired control of MTB infection after HIV infection still provides the best evidence for an important role of CD4 T cells in human anti-MTB immunity.

AIDS Virus induced depletion of CD4 T cells from the air-tissue interphase in the lung

Loss of CD4 T cells during HIV disease progression is brought on by persistent viral replication. Interfering with viral replication by HAART initiation reconstitutes CD4 T cell counts, largely restores pathogen-specific CD4 T cell responses and substantially decreases the risk of developing active TB [29-31]. CCR5-tropic virus variants are responsible for most transmission events and typically prevail until late phase of infection [32]. During natural HIV infection, CXCR4 tropism evolves only relatively late in infection after CD4 T cell numbers have dropped substantially [33] and is associated with infection and depletion of naïve CD4 T cells [34]. Thus, early loss of MTB immune control should usually be linked to CCR5-tropism and selective targeting CCR5⁺ CD4 T cells; CCR5 expression is characteristic of effector memory (EM) CD4 T cells isolated from mucosal tissues including the lung [35-37] and can be induced by antigenic stimulation and activation of CD4 T cells in vitro [38], but is largely absent from naïve CD4 T cells. CCR5-tropic viruses preferentially infect and

replicate in activated memory CD4 T cells that express the chemokine receptor CCR5 and these cells are preferentially depleted after AIDS virus infection [35]. Pathogenesis of CCR5-tropic virus infection has been intensively studied after experimental infection of Simian Rhesus macaques with SIVs - a good model for human HIV infection. Both, acute and chronic SIV and HIV infection results in extensive depletion of EM CD4 T cells from mucosal effector sites, [39-42] including the tissue-air interphase of the lung [36,43]. Hence, EM CD4 T cells at the primary site of aerosolic MTB infection, are also a primary target for depletion after infection with CCR5 tropic viruses and the timing of their depletion after SIV infection is associated with reactivation of MTB infection in macaques [10]. Influx of newly generated CD4 T EM cells can partially replenish CD4 T cells in the air-tissue interphase, despite their reduced life span during SIV infection [36,43-44]. Increased cellular turn over and maturation of central memory (CM) into EM CD4 T cells are responsible for continuous renewal of this EM T cell population and probably simultaneously promote AIDS virus replication in transitional CD4 T cells [45-46], resulting in a net loss of EM CD4 T cell output from secondary lymphoid organs. Progressive loss of the capacity for renewal of this EM CD4 T cell pool is thought to be central to the pathogenesis AIDS virus infection [43]. Substantial and progressive depletion of CD4 T cell within tissue-air interphase is also characteristic for chronic HIV infection humans [47-49]. Human tissue-air interphase CD4 T cells are EM T cells as characterized by a CD45RA-/CCR7-/CD27- phenotype [47-48]. Blocking viral replication by HAART initiation reverses CD4 T cell depletion within tissue-air interphase [49] and reduces the risk- to develop active TB by at least 70% [29]. Together these data demonstrate that the site of primary MTB infection is particularly vulnerable to AIDS virus induced immune defects.

The timing of EM CD4 T cell depletion from the air-tissue interphase after SIV infection is associated with reactivation of MTB infection [10], suggesting that HIV infection can reduce

efficacy of the protective properties of an existing Granuloma [50]. This is supported by histological studies that found differences in the cellular composition, architecture and function of MTB granulomas associated with HIV infection, such as fewer mononuclear cells, fewer CD4 T cell [51-52], perturbations in TNF expression and larger areas of necrosis [51,53]. A more recent study found no such morphological alterations in granulomas during pleural TB during earlier HIV disease stages [53]. Interestingly, granulocyte involvement appears to be increased granulomas from HIV+ subjects, resembling a pattern also observed in MTB infected CD4 knock-out mice [11,23,51]. In summary, relatively little is known about HIV interference with the MTB granuloma. The pathogenic mechanisms of AIDS virus induced granuloma dysfunction need further clarification.

Dynamics of MTB-specific CD4 TH1 cell responses after HIV infection

The timing of disease caused by opportunistic infections is not strictly related to the extent of CD4 T cell depletion for a given pathogen. HIV associated changes in the quantity or quality of opportunistic pathogen-specific CD4 T cell responses could potentially contribute to increased susceptibility to a given pathogen. For example, clinical complications caused by CMV closely correlates with depletion of CMV-specific CD4 T cell responses [54-56]. Similarly, in SIV/BCG co-infected rhesus macaques reactivation of tuberculosis-like disease coincides with waning mycobacterial-specific T cell proliferative responses [27]. Several studies, including our own, have recently shown that MTB-specific CD4 T cell responses are preferentially depleted after HIV infection from circulation and also from the tissue-air interphase [47-48,57] suggesting that HIV MTB-specific Immunity is particularly vulnerable to HIV induced defects. These data support the hypothesis that a reduction in the generation of lung homing MTB-specific EM CD4 TH1 cells after HIV infection is a key factor in the increase risk for development of active TB.

The reasons for differential depletion of different pathogen-specific CD4 T cells after HIV infection are probably multi-factorial. Phenotypic and functional properties of MTB-specific CD4 T cells, such as surface expression of CCR5 [58], a low capacity to secrete “protective” CCR5 ligand Mip-1 β and large capacity for IL-2 dependent T cell proliferation promote cellular HIV infection in vitro and in vivo [57-60]. And indeed, MTB-specific CD4 T cells have significantly higher cell associated Viral loads in vivo as compared to total memory CD4 T cells during active TB [57]. Activated Mycobacteria-specific CD4 T cell responses strongly promote HIV replication both in vitro [59] and in vivo [61-62]. These data support a model, in which a combination of proinflammatory cytokines and cell-contact dependent co-stimulatory interactions maximize transcription of the HIV genome and production of virions in HIV infected antigen-presenting cells, which transmit to responding CCR5+, proliferating MTB-specific CD4 T cells [63-64]. Such a scenario would depend on ongoing MTB-specific stimulation of CD4 T cells during latency. A continuous cross talk between the host immune system and the persisting pathogens [65] would support such a model.

However, the level of antigenic-stimulation during MTB latency is unclear and probably varies between individuals. Loss of MTB-specific CD4 T cell response rather argues against strong antigenic stimulation after HIV infection, because, somehow counterintuitive, MTB-specific CD4 T cells can often be detected in HIV+ subjects with active TB, most probable due to antigen-driven CD4 T cell expansion counteracting (or concealing) depletion. Persistent or expanding MTB-responses after HIV and SIV infection have indeed rather been associated with subsequent progression [58,66-67]. As a consequence, it is difficult to dissect the effects of AIDS virus associated CD4 T cell depletion in the presence of strong antigen-driven cellular CD4 T cell expansion during reactivating TB. In the majority of “latently” infected humans T cell stimulation apparently is insufficient to maintain MTB-specific CD4 T cell responses after HIV infection, implying that other protective mechanisms,

such as “hermetically sealed granulomas” or other immune cell subsets [28] might contain MTB replication. Alternatively, the presence of MTB-specific T cell memory might not necessarily equate with reactivatable disease [29,68-69]. Epidemiological studies are divided: Some studies argue rather for *novo* exposure as compared to reactivation as a frequent cause of HIV associated active TB in high burden settings of sub-Saharan Africa [7], whereas a recent study shows a 5-fold increased TB incidence of HIV+/IGRA+ patients (5%) compared to HIV+/IGRA- patients (<1%), supporting latent MTB reactivation as an important cause for active TB in HIV patients [70]. Thus both mechanisms are likely to play a role. However, it is tempting to speculate that recent exposure and early granuloma formation and maturation is more likely to be affected by HIV interference, as compared to old, mature, “fibrotic and calcified” lesions, which might restrict bacterial dissemination more independent of T cell effector function.

Conclusion

In conclusion, AIDS virus infection interferes with the generation of EM CD4 T cell that home to the primary site of MTB infection – the lung – and dramatically increases risk developing active TB. Moreover, MTB-specific CD4 T cell responses are selectively depleted both, in circulation and at the air-tissue interphase of the lung, and probably further aggravating the failure of the immune system to efficiently control MTB after HIV infection. Other “more global” immune defects brought on by persistent viral replication, such as persistent immune activation or dysfunction and depletion of APCs, are also likely to promote TB disease progression in HIV-infected individuals. Hence at this point in time, early initiation of antiretroviral therapy or the development of an efficacious HIV vaccine would be the best options to reduce morbidity and mortality associated with this co-epidemic.

Key points

- MTB-specific CD4 TH1 cell responses are critical for immune control of tuberculosis in the murine MTB infection model.
- Effector Memory CD4 T cells within the primary site of MTB infection - the air-tissue interphase of the lung - are a major target for depletion after AIDS virus infection.
- The extent of CD4 T cell depletion from the air-tissue interphase during acute SIV infection is associated with early disease reactivation in macaques with latent MTB infection.
- MTB-specific CD4 T cells are preferentially depleted from circulation and from the air-tissue interphase in TB asymptomatic subjects after HIV infection.
- Depletion of CD4 T cells, particularly EM CD4 T cells and MTB-specific CD4 T cells within the air-tissue interphase, might be a key factor in the impaired control of MTB infection after HIV infection.

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Figure legends

Figure 1. Estimated Tuberculosis incidence rates, 1990 – 2010. Global and African trends in estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands. Figure was adapted and modified from the WHO Report 2011 Global tuberculosis control.

Figure 2. Proposed mechanism of how HIV induced CD4 T cell depletion impairs immune control of MTB infection.

1. Infection of airways with MTB (red rods); the bacilli are taken up by alveolar Macrophages (pale orange) and dendritic cells (DCs, dark orange). MTB-infected DCs then migrate to the thoracic lymph nodes to trigger the adaptive MTB-specific CD4 T cell response. Some MTB-infected DCs are co-infected with HIV.

2. Within the lymph node, HIV is efficiently transferred from DCs to MTB-specific CD4 T cells that respond to cognate antigen. DC-T cell interaction maximizes HIV virion production in antigen-presenting cells and simultaneously increases CCR5 expression by activated MTB-specific CD4 T cells (pink). IL-2 dependent cell cycling promotes complete reverse transcription of the viral RNA genome and as a consequence productive HIV infection of MTB-specific CD4 T cells. Non-cycling CD4 T cells (blue) in close vicinity/contact to productively infected cells also die as a result of abortive HIV infection.

3. HIV infection reduces the output of lung homing Effector Memory and particularly MTB-specific CD4 T cells.

4. MTB-specific EM CD4 T cells home to the lung, the primary site of MTB infection. HIV reduces the overall number of lung homing MTB-specific EM CD4 TH1 cells and shortens cell survival of EM CD4 T cells. As a consequence T cell mediated granuloma formation, maturation and thus the control of MTB infection is impaired leading to an increased risk to develop active TB upon new MTB infection.

4B. In HIV infected humans with latent MTB infection, reduced delivery of MTB-specific CD4 TH1 cells decreases functionality of the MTB granuloma and promotes escape of MTB from the granuloma and increases the risk of systemic dissemination of MTB infection. It can be speculated that more mature, fibrotic granulomas might contain MTB infection more independently from CD4 T cell depletion.

Recommended literature

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Figure 1

2. Transfer of HIV from DCs to proliferating MTB-specific EM CD4 T cells at the thoracic lymph node