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MINIREVIEWS

Mechanistic insights on immunosenescence and chronic immune activation in HIV-tuberculosis co-infection

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Abstract

Immunosenescence is marked by accelerated degradation of host immune responses leading to the onset of opportunistic infections, where senescent T cells show remarkably higher ontogenic defects as compared to healthy T cells. The mechanistic association between T-cell immunosenescence and human immunodeficiency virus (HIV) disease progression, and functional T-cell responses in HIV-tuberculosis (HIV-TB) co-infection remains to be elaborately discussed. Here, we discussed the association of immunosenescence and chronic immune activation in HIV-TB co-infection and reviewed the role played by mediators of immune deterioration in HIV-TB co-infection necessitating the importance of designing therapeutic strategies against HIV disease progression and pathogenesis.

Key words: Cluster of differentiation 38; Human immunodeficiency virus-tuberculosis co-infection; Immunosenescence

Core tip: The mechanistic aspects associated with increased expression of senescence and immune activation markers cluster of differentiation (CD) 38, CD69, CD57, human leukocyte antigen-DR, and the down-regulation of functional molecules, *viz.*, CD28, CD27, CD40L and CD127 on human immunodeficiency virus-specific T cells appear to be crucial in the immunopathogenesis of HIV-tuberculosis (HIV-TB) co-infection. *Mycobacterium tuberculosis* appears to play a major role in accelerating HIV disease progression, by directly or indirectly facilitating factors associated

with immune senescence. Measures to ameliorate immunosenescence and immune activation appear to stem from identification of novel targets of downstream senescence signaling. Restoration of molecules associated with T-cell homeostasis, differentiation, cell survival and proliferation abilities of HIV-specific $CD8^+$ T cells is key to foster functional immune responses.

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INTRODUCTION

The hallmark of human immunodeficiency virus type 1 (HIV-1) disease is the destruction of cluster of differentiation (CD) 4^+ T cells eventually leading to the failure of functional attributes of the host immune system in containing viral establishment. The key target cells of HIV infection are $CD4^+$ T cells, dendritic cells (DCs), monocytes/macrophages, thymocytes and microglial cells[1,2]. HIV enters these cells *via* binding primarily but not limited to target receptors/coreceptors CD4, chemokine coreceptor 5 (CCR5) and CC-chemokine receptor 4 (CXCR4)[3-5]. The CCR5-tropic HIV (macrophage-tropic R5 strain) appears to predominate primarily during the onset of infection, and eventually the CXCR4 HIV (T cell-tropic X4 virus) takes over to establish a chronic phase leading to eventual destruction of $CD4^+$ T cells harnessed by the onset of opportunistic infections and neoplasms[6].

HIV reportedly evades the immune system through several ways to effect direct or indirect killing of infected and uninfected cells[7]. HIV facilitates $CD4^+$ T cell depletion primarily *via* accelerated destruction, chronic immune activation (CIA) and also by impairing the regeneration of new T cells from existing T-cell precursors[8]. Evidence suggests that monocytes and macrophages although may not be significantly affected in HIV-infected individuals, their role as reservoirs for HIV-1 provides homes for long-term survival following infection and can therefore be transmitted to bystander T cells[9,10]. DCs contribute even more to HIV-1 pathogenesis and studies have reported reduced levels of peripheral blood DCs in HIV-1 patients and changes in their phenotypic and functional properties[11]. Evidence also suggests that HIV could alter the expression of costimulatory molecules as well as chemokine receptors[11]. HIV-1 infected DC in contact with T cells fail to provide optimal feedback to T cells partly due to impaired release of IL-12, which in turn fail to provide optimal survival signals for DCs owing to impairment in the expression of CD40L on T cells. Furthermore, sustenance of T-cell proliferation is also impaired due partly to decreased secretion of IL-2 by activated T cells[12,13].

IMMUNOSENSESCENCE AND CHRONIC IMMUNE ACTIVATION - KEY CULPRITS OF HIV DISEASE PROGRESSION

Immunosenescence is a common biological phenomenon occurring in elderly individuals, and represents gradual deterioration of the immune system leading to attenuated responses to infections and vaccinations[14]. Roy Walford was the first to use the term "immunosenescence" in 1969. He believed that normal ageing in humans and animals is related to deficient immune functions[15]. Like any other cells in the body, immune cells undergo senescence. Immune senescence is characterized by changes in T-cell subsets, molecular alterations and often involves atrophy of lymphoid organs, eventually culminating in the decline of T- and B-cell functions[16]. Recent studies have shown that immunosenescence can occur involving both the adaptive and innate arms of the immune systems[17]. However, the major immune cells severely affected by immunosenescence are the T cells, which ultimately result in compromised responses to antigens and increased rates of differentiation of naïve T cells to terminally-differentiated T cells[18,19].

Immunosenescence is marked by accelerated degradation of immune system with increased turn-over of senescent T cell phenotypes showing remarkable ontogenic defects[20]. The cells possess reduced life-span with shorter telomere lengths, reduced proliferation abilities, dysfunctional cytokine-secreting abilities, deficient anti-viral responses (exhausted effector T cells), and suppression of T-cell responses due to expansion of suppressor T cells and up-regulation of multiple negative immune receptors[21-25]. Currently, there is increasing evidence of the expansion of senescent T cells expressing surface markers such as CD28, CD27, CD57 and CD127, especially in HIV and cytomegalovirus (CMV) infections[26-30]. This suggests that persistent viral infections (PVIs) can induce the expansion of senescent T cells *via* a mechanism called "replication senescence" or "Hayflick phenomenon", also defined as the decrease in the ability of a cell to proliferate, with significant mark of terminal differentiation[31,32].

Interestingly, immunosenescence also appears to occur in younger individuals with underlying malignancies and autoimmune conditions. An overwhelming body of evidence shows that persistent microbial infections with highly sustained levels of chronic antigenic stimulation, especially with HIV and CMV, could lead to functional impairment of Ag-specific T cells including proliferative abilities[33]. Furthermore, premature senescence of $CD4^+$ and $CD8^+$ T cells is well-characterized in chronic HIV infection with evidence of up-regulated surface markers and functions similar to that seen in elderly HIV-uninfected individuals[34,35]. Chronic HIV-infected patients have also shared some similarities in T-cell dysfunction with that of 'healthy' aging elderly[36,37]. Interestingly, the persistence of immune activation is exceptionally notable in chronic HIV disease both in mono-infected and co-infected with

other infectious agents such as HCV, HBV and MTB, despite that highly-active antiretroviral therapy suppressed viral replication in these subjects[38-40]. This phenomenon appears to be attributed to the up-regulation of immune activation markers namely ki-67, CD38, human leukocyte antigen - DR (HLA-DR), and CD69 on HIV-specific $CD4^+$ and $CD8^+$ T cells[41,42]. Of these, CD38 expression has been reported to serve as a reliable marker of disease progression and acquired immunodeficiency syndrome (AIDS)-associated mortality[43].

Markers of CIA apart from T cells, are also expressed in a plethora of other immune cells such as monocytes, DCs, and natural killer (NK) cells[44]. Elevated immune activation of T cell appears to be one of the potent predictors of HIV disease progression[45,46] as highly sustained immune activation may contribute to rapid disease progression by impairing the ability of the immune system to respond to antigens[47], suggesting that CIA could be a key player in HIV pathogenesis and indirectly predicts progression to non-AIDS related morbidity and mortality[34]. Accumulating line of evidence also suggests that increased expression of CD57 and reduced levels of CD127 in patients with CIA highly correlated with T-cell dysfunction and senescence[26,27,48,49] supporting the notion of potential association between CIA and immunosenescence, especially in T cells.

IMMUNOSENESCENCE AND HIV-TB CO-INFECTION

Current investigations in human HIV/TB co-infection have provided several fundamental principles to understand how these distinct pathogens additively interact to accelerate the rates of disease progression. Although the precise mechanism of co-pathogenesis still remains elusive, it has widely been shown that both TB and HIV exert substantial influence on the host immune system. Hence, investigations underpinning the influence of TB in HIV/TB co-infection, and the importance of T-cell responses to elucidate the mechanisms underlying the failure of the immune system resulting from the dreadful interaction between HIV and TB are urgently required.

While it is increasingly becoming clear that persistent HIV disease facilitates the onset of CIA and consequently to premature senescence[20,24,28,45,47,50], existing hypotheses suggest that MTB exacerbates HIV disease by enhancing viral transmission and entry into immune cell by causing alternations in signal transduction, cytokine modulation; overcoming anti-viral responses with overwhelming HIV promoting responses; and facilitating HIV amplification by rendering the formation of granuloma[51-54]. The up-regulation of immunosenescence markers on T cells appears to accelerate the depletion of functional T cells, hastening a shift to terminally-differentiated T cells with altered immune functions[55], and hence we speculate that this potentially might facilitate the onset of AIDS, and disseminated and extra-pulmonary TB infections. Based on this mechanistic viewpoint it is also possible to correlate immunosenescence with CIA in HIV-TB co-infection.

CD38 AND HLA-DR - IMMUNE ACTIVATION MARKERS IN HIV-TB CO-INFECTION

CD38 and HLA-DR have been widely used to deduce the activation status of various immune cells, apart from other markers such as CD27, CD28, Ki-67 and CD69[41,42]. CD38 is a glycoprotein receptor found on the surface of T cells, B cells and NK cells with key roles in signal transduction and calcium mobilization associated with their activation[56]. On the other hand, HLA-DR is an major histocompatibility complex class II molecule that presents antigens to APCs and acts as a marker of T-cell stimulation and activation[56-58]. Numerous literatures have established that immune activation is a direct measure of HIV disease progression[45,59-61], which has previously been shown with CD38 expression on $CD8^+$ T cells[43,46,62]. Multiple studies have also shown that concomitant with HCV, HBV, and MTB can directly impact HIV disease progression with excessive T-cell activation in the peripheral blood[40,63-65]. Increased expression of CD38 on both $CD4^+$ and $CD8^+$ T-cells of HIV-TB co-infected subjects has been described relative to HIV mono-infection[63,66,67]. This was also consistent with existing evidences that explain the association of HIV/TB co-infection with sustained levels of peripheral activation in immune compartment following pathogenic persistence[67-69]. Indeed, TB infection fosters immune activation as evident from up-regulated CD38 expression on T-cell subsets as compared to uninfected subjects[66,70]. Besides this, CD38 expressions in both the $CD4^+$ and $CD8^+$ T-cell subsets have been inversely correlated with $CD8^+$ T-cell counts and HIV plasma viral load, and that enhanced CD38 expression could lead to rapid HIV disease progression[66,70]. The mechanism whereby MTB appears to attenuate the expression of HLA-DR, particularly on innate cells such as macrophages and DCs, is *via* the synthesis of bacterial proteins (such as 19kD lipoprotein and lipoprotein rG), which subsequently cause impaired antigen presentation and processing, potentially affecting the downstream signaling for HLA-DR expression on T cells[71-74]. In addition, MTB can evade phagocytosis by macrophages and eventually delay the onset of adaptive immune responses[75,76]. Active MTB infection can suppress the expression of HLA-DR *via* innate receptors (*i.e.*, TLR2), gene repression (*i.e.*, histone deacetylation), and cytokine-mediated inhibition (*i.e.*, IFN-γ) in infected individuals.

HOW DOES HIV-TB CO-INFECTION ENGINEER THE DIFFERENTIATION OF SENESCENT PHENOTYPES?

Cellular differentiation is the process by which a less specialized cell becomes a more specific phenotype with

unique functions. Upon antigenic stimulation, naïve T cells are activated and undergo differentiation into various subsets that possess distinct functionalities. CCR7 and CD45RA are two markers of T-cell differentiation but many others do exist, with two intriguing co-stimulatory molecules, CD27 and CD28[16]. Others have proposed a model of differentiation using co-expression of CD27 and CD28 to subdivide $CD8^+$ T cells into three distinct subsets based on their proliferation history, *viz*., early ($CD28^+CD27^+$), intermediate (CD28-$CD27^+$), and late ($CD28^-CD27^-$) T-cell subsets[77]. Subsequent research also showed that intermediate-differentiated $CD4^+$ T-cell subsets lose CD27 prior to CD28 ($CD28^+CD27^-$)[36,78]. CD27 and CD28 has also been reported to indicate the stage of T-cell activation and proliferation[79,80]. Lowered expression of CD28 indicates immunosenescence, marked by shortened telomeres and diminished replicative abilities[81], whereas CD27 has been recently characterized as a modulator of T-cell functions, and has been suggested as a better correlate of proliferative potentials[55]. Late-differentiated subsets have been associated with strong cytotoxic potentials, and gradual up-regulation of CD57 expression suggesting a closer relationship between senescence and differentiation[77]. It has also been established that persistent infections might lead to loss of CD27 and CD28, which reflects that more proliferation cycles have taken place in response to pathogens, eventually leading to increased T-cell activation and advanced stages of differentiation[82,83]. Hence, HIV-TB co-infection appears to have a synergistic effect in down-regulating CD27 and CD28 in accelerated rate as in HIV mono-infection.

Research also shows that persistent HIV infection impacts the differentiation of $CD8^+$ T-cell subsets resulting in the over-presentation of intermediate-differentiation stage[84,85]. This could largely be due to a block in maturation of $CD8^+$ T cells engineered by HIV to maintain chronicity leading to ineffective cytokine and cytotoxic responses following antigenic stimulation[85-87]. Hence it is speculated that MTB may be involved in accelerating T-cell differentiation despite the blockade of maturation exerted by HIV, leading to biased distribution of advanced stage of differentiation.

ROLE OF CD57 AND CD127 IN IMMUNE CELLULAR SENESCENCE

CD57 is a marker of senescence that has been associated with *in vitro* replicative senescence, or proliferation incompetence in both $CD4^+$ and $CD8^+$ T cells of healthy elders as well as PVIs[48,88,89]. Extensive investigations have also been carried to decipher the functional role of CD57 in apoptosis, activation-induced cell death, senescence and overwhelming cytokine and cytolysin responses. Outside HIV infection, CD57 has also been associated with various diseases and cancers[88]. Both HIV and MTB alone have been shown to facilitate the expansion of $CD57^+CD8^+$ T cells with wide range of functionality changes and contributing to the immunpathogenesis of each disease progression[48,90]. Furthermore, expansion of $CD57^+CD8^+$ T cells upon stimulation by MTB have more extensive cytokine and cytolytic potential with secretion of TNF-α and IL-6[53], and this abnormality of modulation may eventually promote HIV manifestation in co-infected individuals.

Based on our understanding, immunosenescence is best characterized by T cells showing increased CD57 and decreased CD28 expressions, also known as "late-differentiated" or senescent cells, despite several studies have proposed that co-expression of CD57 and CD27 may be a better correlate compared to CD28 as an indicator of replicative senescence[55,87]. It is also evident that loss of CD27 and CD28 with concurrent up-regulation of CD57 descriptively represents increase of replicative inability when T cells differentiate further[24,91]. Co-infection appears to foster the expansion of late "senescent" $CD8^+$ T cells ($CD57^+$ CD28/$CD27^-$) compared to early "senescent" $CD8^+$ T cells ($CD57^-$CD28/$CD27^+$), whereas HIV mono-infection has over-presentation of intermediate "senescent" $CD8^+$ T cells ($CD57^-CD28^-/CD27^-$). Hence, given that late "senescent" $CD8^+$ T cell is associated with decreased telomerase activity with the shortest telomere length, and a reduction in activation-induced activation[92], there appears to be more turnover of late-differentiated $CD8^+$ T cells in co-infected individuals with expanded expression of CD57, which suggests that more T cells have reached the stage of true senescence[93].

CD127 has been indicated in activation, homeostasis, differentiation, and cell survival of different T cell populations[94,95]. Decrease of CD127 expression has been associated with HIV disease progression[49,96]. The importance of maintenance CD127 for T-cell survival, especially during chronic HIV infection has also been suggested[27]. The down-regulation of CD127 may ensue due to several mechanisms, one involving HIV infection where there is a dysfunctional cytokine response when excessive IL-7 may cause an inhibitory effect on CD127 expression; while the other may be due to imbalance of IL-7 levels in the peripheral circulation[97,98].

CONCLUSION

Despite the disparity in pathogenesis and natural history HIV-TB disease, current literature suggest that both the pathogens harness a higher quantum of symbiotic impact on each other leading to accelerated rates of deterioration of host's immune responses. Existing understanding of pathogen interaction based on immunology research has contributed to genesis of several novel hypotheses to precisely address how contemporaneous manifestations of HIV aggravate TB disease progression and vice versa[51]. However, these evidences have not been conclusively successful in deciphering the mechanism underlying the role of MTB and HIV in accelerating immune deterioration. A better understanding of immunosenescence, and the development of strategies aimed to rejuvenate T cells, especially in PVIs will direct to improved quality of life of infected individuals. In addition, extension of knowledge

on immunosenescence to precisely identify therapeutic targets and surrogate biomarkers to validate senescence phenomena as clinical endpoints may be key to better healthcare requirements.

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