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Review

Immune response and possible causes of CD4$^+$T-cell depletion in human immunodeficiency virus (HIV)-1 infection

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This review work examines immune response and possible causes of depletion of CD4$^+$ T-cells in patients with human immunodeficiency (HIV)-1 infection. HIV has been accepted as a global problem however, the developing countries are the most affected by the epidemic. Countries in the sub-Saharan Africa seem to bear the bulk of the HIV burden among the developing countries with about 24.7 million (almost 63%) of all people living with HIV globally in 2006 live in sub-Saharan Africa. The major factor obstructing progress towards an effective vaccine to prevent or modulate HIV-1 infection is that the critical features needed for a protective immune response are not fully understood. Although, it has been found that potent neutralizing antibodies can protect against experimentally acquired HIV infection in animal models, they are scarcely generated *in vivo* in the infected person and neutralization resistant viral variants have been noticed to develop rapidly in chronic infection. It is generally believed that cellular immune responses, particularly specific cytotoxic T lymphocytes (CTL), are important in the host response to HIV-1 infection. Scientists have observed that CTL develop very early in acute HIV-1 infection, coincident with a rapid fall in plasma vireamia, whereas in chronic infection their levels are inversely related to viral load. However, the powerful HIV-specific CTL response ultimately fails to control HIV replication. This could be due to the emergence of viral variants that escape CTL recognition or impairment of CTL function.

Key words: Immune system, immune suppression, virus-mediated cell destruction, chronic infection.

INTRODUCTION

Available report has shown that untreated HIV disease is characterized by a gradual deterioration of immune function. Most prominently, the CD4$^+$ T-cells are disrupted and destroyed during the typical course of HIV infection. It is known that the CD4$^+$T-cells (T -helper cells) play a major role in the immune response, signaling other cells in the immune system to perform their specific roles (Deeks et al., 2004; Brenchley et al., 2004; Ondoa et al., 2005).

It has been shown that a healthy, HIV-negative person usually has 800 to 1,200 CD4$^+$ T -cells per mm^3 of blood.

During untreated HIV infection, the number of these cells in a person's blood progressively declines. When the CD4$^+$ T cell count falls below 200 mm^{-3}, a person becomes particularly vulnerable to the opportunistic infections that are commonly associated with AIDS (the end stage of HIV disease). Most scientists believe that HIV causes AIDS by inducing the death of CD4$^+$ T cells or interfering with their normal function and by triggering other processes that weaken a person's immune system. For example, the network of signaling molecules that normally regulates a person's immune response is interrupted during HIV disease, impairing a person's ability to fight other infections. The HIV-mediated destruc-tion of the lymph nodes and related immunologic organs also plays a major role in causing the immunosuppres-

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sion seen in people with HIV infection (Dandekar, 2007; Vajpayee et al., 2009).

$CD4^+$T-cell and its significance

The $CD4^+$ is a molecule found primarily on the surface of helper T-lymphocytes. The designation CD stands for "Cluster of Differentiation" and refers to a nomenclature applied by immunologists who are involved in the business of generating monoclonal antibodies against surface proteins of blood cells as a means of identifying the surface proteins and studying them. When a "cluster " of monoclonal antibodies (antibodies produced *in-vitro* by single clones of B-lymphocytes) is found to react with the same protein, it represents a group of reagents defining a specific marker and that marker is given a CD number (SAHIVCS, 2001; Choudhry et al., 2007; Appay and Sauce, 2008).

Functions of $CD4^+$T-cell

The $CD4^+$ molecule is also the main receptor involved in combating HIV-1 infection and docks with the glycoprotein 120 (gp120) found on the envelope of the HIV-1 viral particle. The $CD4^+$T-cells perform a central and coordinating role in the immune response (Hughes et al., 1997; Vajpayee et al., 2005, Vajpayee et al., 2009). These cells, also known as T4 or helper/inducer T lymphocytes, recognize antigens presented by cells bearing HLA class 11 molecules such as monocytes and macrophages. The $CD4^+$molecule help to stabilize the binding of these T-lymphocytes to the HLA 11 molecule on the antigen-presenting cell (Wilson, 1990; Savarino et al., 2000; Wilson et al., 2004) . Once an antigen is recognized, $CD4^+$T lymphocytes orchestrate the body's antigen- specific immune response and specific functions of $CD4^+$ T lymphocytes include the following:

(1) Coordinating B-lymphocyte production of antibodies to these antigens.
(2) Producing cytokines.
(3) Induction of cytotoxic lymphocytes.

These functions make $CD4^+$ T lymphocytes critical elements of the immune system and their dysfunction and destruction in HIV-1 infection seriously impairs the ability to respond to diverse pathogens (Bowen et al., 1995; SAHIVCS, 2001; Vajpayee et al., 2005).

Progressive destruction of the immune system in advanced HIV Infection

In the absence of suppressive antiviral therapy, HIV infection advances and progressively infects more cells in the follicular dendritic cell (FDC) network, resulting in the destruction of lymph node architecture. This promotes the release of more viral particles into the circulation (SAHIVCS, 2001). The release of HIV into circulation causes $CD4^+$T-cells to be infected and destroyed at a faster rate than can be replaced, thereby shifting the dynamic equilibrium in favour of the virus (Wei et al., 1993; Ho et al., 1995; Chun, et al., 1997; Savarino et al., 2000; Leng et al., 2001). Studies have shown that an important cause of declining $CD4^+$T-cell counts is the failure of the regenerative capacity of the immune system to produce immune cells (Ho et al., 1995; Zhang, 1998; Hazenburg et al., 2000; Ondoa et al., 2005). This is a result of HIV infection of precursor stem cells and is also due to failure of "programming" of $CD4^+$ T-cells in the HIV-infected thymus gland. This culminates in the destruction of the immune system and consequent failure to mount immune responses that are adequate to prevent oppor-tunistic infection and/or neoplasmic disease (Wei et al., 1993; Ho et al., 1995; Roederer, 1995; Oguntibeju et al., 2004; Oguntibeju et al., 2007a, b).

Dynamic equilibrium between $CD4^+$T-cell production and clearance

The initial process in the life cycle of HIV infection is the binding of HIV glycoprotein (gp120) that is present on the surface of the virus to $CD4^+$ molecule (McDougal et al., 1996; Bentwich et al., 1999; Bialecki et al., 2009). Once the virus gains entrance into the cell, it begins the process of viral replication following binding to $CD4^+$T-cell and fusion with the cell membrane. A direct cytopathic effect of HIV on $CD4^+$T-cells may occur via the destruction of the cell membrane that is subsequent to massive viral budding (Rowland- Jones et al., 1997; Denny et al., 1998), the presence of large amounts of non- integrated viral DNA, heterodisperse RNAs and viral core proteins in the cytoplasm of the infected cell that interferes with proper cell function, and the complexing of HIV gp120 with intracellular $CD4^+$ molecules (Weiss, 1996; Hughes et al., 1997; Eggena et al., 2005; Appay and Sauce, 2008).

The depletion of $CD4^+$T-cells may also be due to the destruction of precursor cells that give rise to $CD4^+$T-cells *in vivo* or cells which produce factors essential for $CD4^+$T-cell growth (Rosenberg and Fauci, 1990; Eggena et al., 2005; Kaushik et al., 2006). An alternative mechanism for $CD4^+$T-cell depletion involves the formation of short-lived multinucleated giant cells or syncytia between an HIV-infected $CD4^+$T-cell and a cluster of uninfected $CD4^+$T-cells. It has been estimated that between 100 million and 10 billion virus particles are produced and cleared every 24 h. Thus, virus production occurs not only during the primary and advanced stages of the disease (typically symptomatic) but also during the intermediate stage of the infection (the virus is not truly latent) (D'Souza and Haden, 1996; Wong et al., 1997; Kaushik et al., 2006).

At the intermediate stage of HIV infection, levels of the virus in the plasma are the result of a dynamic equilibrium between the production of HIV and its clearance by the immune system. In this continuous turnover of the virus population, about 50% of the circulating virus is suggested to be replaced with newly produced virions daily (Young, 1997; McCune, 2000; Leng 2001; Ondoa et al., 2005). The extensive production of HIV is closely related to the destruction and replacement of $CD4^+$T-cells. Scientists have estimated that the half-life of HIV-producing $CD4^+$T-cells is about 1.2 days and between 1 and 2 billion new $CD4^+$T-cells are produced every day (Pantaleo et al., 1998; Ondoa et al., 2005; Kaushik et al., 2006). There appears to be a difference between the half-lives of various populations of HIV-infected cells. It is said that productively infected $CD4^+$T-cells constitute a short-lived population (about 1.2 days), while other HIV-infected cells, for instance macrophages, and constitute a long-lived population with an average half-life of 14 days (Young, 1997; Wong et al., 1997; Pantaleo et al., 1998; Bialecki et al., 2009; Vajpayee et al., 2009).

HIV Attacks the immune system via the $CD4^+$T-cell

HIV attacks the immune system by targeting the heart of the immune system, the $CD4^+$T-cells which are the conductors of the immune system. When a pathogen is introduced into the body as either a virus or a bacterium, it is first recognized by $CD4^+$T-cells. The $CD4^+$T-cells are responsible for coordinating each of the host immune defences, namely the killer cells, the antibodies and the phagocytes that will eliminate the pathogens (Autran and Katlama, 2000). However, if the $CD4^+$T-cells are destroyed, the immune defences that remain become less functional and are unable to eliminate the pathogens and the latter can proliferate to cause disease (Autran and Katlama, 2000). In the body, HIV is replicating in its niche, which is the memory $CD4^+$T-cells-the cells that are very actively mobilized against the most current infections. Each time a memory $CD4^+$T/cell is infected by HIV and each time HIV is replicating in a memory $CD4^+$T-cell, this cell dies and is eliminated. In the healthy young adult or at the beginning of the HIV infection, these dying memory $CD4^+$T-cells are replaced by a constant source or a reservoir of naïve $CD4^+$T-cells originating from the thymus. It is reported that during the course of HIV infection, about one billion HIV particles are produced per day, resulting in increasing numbers of infected $CD4^+$T-cells. The infection spreads in the memory cells, in the naïve $CD4^+$T-cells and in the thymus; the source is therefore progressively exhausted, surpassing the capacity to produce new $CD4^+$T-cells (Autran, 2000; Appay and Sauce, 2008).

It has been shown that progressive loss of $CD4^+$T-cells is the cardinal manifestation of the effects of HIV infection. The $CD4^+$T-cell count can therefore serve as a useful indicator of the severity of the infection, providing both a convenient measure of immunological status and giving some indication of the risk of opportunistic infections and neoplasia, particularly in individuals who have already begun to show a substantial $CD4^+$T-cell decline. The $CD4^+$T-cell count indeed has considerable importance in some systems used to stage HIV infection and by implication the guidance of treatment decisions. It is particularly important in determining whether it is appropriate to initiate prophylactic therapy for opportunistic infections (Bagasra et al., 1992; Hughes et al., 1997; Dandekar, 2007; Appay and Sauce, 2008). The significance of the destruction of $CD4^+$T-cells in an HIV-infected person becomes evident when their functions are considered.

$CD4^+$T-cell Depletion in HIV disease

In many parts of the world, infection with the HIV leads to AIDS and then to death if not treated. In time, it became clear that the virus could replicate within human $CD4^+$T-cells *in vitro*, that the viral envelope protein could bind to $CD4^+$T-cell and circulating $CD4^+$T-cells decreased in number as the disease progressed (Martin, 2000). It was also apparent that $CD4^+$T-cells were crucial in coordinating cellular and humoral immune responses against exogenous antigens. As a result of these observations, it was not difficult to imagine that HIV-associated immunodeficiency was due to virally mediated destruction of $CD4^+$T-cells (Stuart et al., 2000; McCune, 2001; Choudhry et al., 2007).

Evidence for $CD4^+$ T-cell depletion

There is a growing realization that the T-lymphocyte compartment comprised multiple subpopulations and that there are inadequate means by which to monitor the relative growth, death and movement of these subpopulations in an individual patient over time. The definition of $CD4^+$T-cell loss in HIV disease thus remains unclear (McCune, 2001; Deeks et al., 2004; Brenchley et al., 2004; Dandekar, 2007). Most researchers agree that HIV infection results in the progressive loss of $CD4^+$T-cells from circulation as well as the depletion of $CD4^+$T-cells from total body stores (Haase, 1999; Wong et al., 1997; Martin, 2000). Quantitative estimates, using a variety of assumptions, indicate that the normal young adult (<30 year old) harbours about 2×10^{11} mature $CD4^+$T-cells (Haase, 1999; Dandekar, 2007). In the HIV-infected patient, this total number is halved by the time the peripheral blood $CD4^+$T-cell count falls to 200 cells/ml. As the HIV infection progresses to a more advanced stage, destruction of parenchymal lymphoid spaces is so extensive that enumeration of the total body $CD4^+$T-cell count has not been attempted. With further disease pro-

gression, there is also a decrease in the proportion of resting naïve ($CD45RA^+CD62L^+$) T-cells and an increase in the proportion of activated memory/effector ($CD45RO^+$) T cells; concomitantly, the T-cell receptor (TCR) repertoire is both perturbed and restricted. Among those cells that persist, many may be dysfunctional. On the whole, HIV induces both quantitative and qualitative defects in the $CD4^+$T-cell compartment and the circulating $CD4^+$T-cell count continues to be one of the best surrogate markers by which to gauge prognosis in late infection and to trigger treatment interventions (Haase, 1999; McCune, 2001; Vajpayee et al., 2009; Bialecki et al., 2009).

Possible causes of $CD4^+$ T-cell depletion

Several mechanisms have been proposed to explain HIV-mediated depletion of $CD4^+$T-cells. All are based on experimental observations (Martin, 2000; McCune, 2001). The total body $CD4^+$T- cells may be depleted in absolute number because they are destroyed or because their production is impaired. In addition, the fraction of circulating cells may decrease if viral infection results in their redistribution out of the intravascular space and into the confines of lymphoid organs (McCune, 2001; SAHIVCS, 2001; Appay and Sauce, 2008).

The balance of destruction and production is one important factor that can be explained by multiple mechanisms. It is possible, for example, that $CD4^+$T-cell depletion is related directly to the virally mediated destruction of infected cells. On the other hand, physiological responses to HIV infection might initiate events that result in the destruction of uninfected cells. In either case, loss of mature cells should be compensated for by increased production of new cells and mature $CD4^+$T-cell depletion should occur only if cells lost in the periphery cannot be replaced. The devastating feature of HIV infection is that the virus can have direct and indirect pathogenic effects on both mature $CD4^+$T-cells and on the progenitor cells from which they arise (McCune, 2001; Brechley et al., 2004; Choudhry et al., 2007). To provide further in sight into and explanation for $CD4^+$T-cells depletion, Ho et al (1995) proposed the tap and Drain hypothesis. According to this mechanism, $CD4^+$T-cell production (a wide –open tap) is not balanced by the huge daily loss (the drain) of $CD4^+$T-cells as a consequence of HIV infection.

Accelerated destruction of mature $CD4^+$T-cells

Early experiments done with laboratory-adapted HIV isolates in tissue culture revealed a cytopathic virus with exquisite tropism for $CD4^+$T-cells. The provision of potent (protease inhibitor-containing) antiretroviral medications to patients with advanced HIV disease caused the viral load to drop and the $CD4^+$T-cell count to rise. By making reasonable and largely accepted assumptions about T-cell distribution and by assuming that antiretroviral therapy does not alter the production rate of T-cells, the statement was interpreted to mean that, before therapy, continuous rounds of infection sustained the viral load and that as many as 2×10^9 infected $CD4^+$T-cells were destroyed per day. By extension, HIV disease is a high state, accelerated destruction of mature $CD4^+$T-cells leads to eventual exhaustion of the immune system (Ho et al., 1995; Wei et al., 1993; Deeks et al., 2004). In HIV-infected human subjects, quantitative image analysis revealed decreased numbers of $CD4^+$T-cells and increased levels of cellular proliferation and apoptosis in lymphoid tissue (Ho et al., 1995; McCune, 2001; Hazenberg et al., 2003; Wilson et al., 2004).

Chronic activation and $CD4^+$T-cell death

It is agreed that $CD4^+$T-cell death may occur in uninfected cells as a by-product of HIV infection of other cells. According to Grossman and Herberman (1997), HIV disease is typified by a state of chronic activation driven in part by the antigenic stimulus of HIV and in part by an antigen-independent mechanism. For instance, cytokines are released by apoptotic cells and activated T-cells. Multiple bursts of activated cells spread throughout the body and would be characterized by apoptotic cell-mediated activation of resting lymphocytes, cytokine-driven expansion of responding cells and contraction of the responding population by activation-induced cell death. It is believed that if apoptotic cells are infected by or otherwise carry HIV, antigen- specific cell activation could support virus dissemination to responding $CD4^+$T-cells, irrespective of their TCR specificity (Pope, 1994; hazenberg et al., 2003; Ondoa et al., 2005). In turn, the virus may be spread upon activation of non-productively infected $CD4^+$ memory T- cells in the context of immune responses to HIV or other antigens. During the asymptomatic phase of infection, when the fraction of infected cells is much lower than the fraction of activated cells, these bursts would predictably continue in a local, recurrent and asynchronous fashion, and $CD4^+$T-cell depletion might be driven by several mechanisms (Bentwich et al., 1999; Ondo et al., 2005) . It has been suggested that the activation of naïve cells into the activated/memory pool may not be fully compensated for by replenishment of new naïve cells from the thymus or by the generation of viable memory cells (Hazenberg et al., 2000, 2003). Alternatively, chronic stimulation of resting T-cells might have a negative effect on the homeostatic regeneration of these cells. The relevance of this process to $CD4^+$T-cell depletion is underscored by the observation that disease progression is associated with immune activation and vice versa (Wilson, 1990; Bentwich et al., 1999; Hazenberg et al., 2003; Vajpayee et al., 2005).

Grossman et al. (2002) immune activation hypothesis which proposes that HIV adopted strategies to increase the availability of target cells by activating $CD4^+$T-cells. Thus, it could be argued that increasing target cells may be likened to fueling a fire, consequently causing more viral replication and runaway depletion of $CD4^+$T-cells. In a recent study, Yates et al. (2007) investigated the correlation between the runaway $CD4^+$T-cell depletion process and the slow scale of memory $CD4^+$T-cell depletion in persons with HIV infection. To explain the depletion of $CD4^+$T-cells by activation hypothesis as proposed by Grossman et al (2002), Yates et al. (2007) suggested that immune activated $CD4^+$T-cells have a very short life span which shows that immune-activated $CD4^+$T-cells are lost by activation-induced cell death. Thus, Yates and colleagues (2007) demonstrated that the immune activation model provides an explanation for the depletion of $CD4^+$T-cells and that the rate of destruction is dependent on the immune activation rate.

Impaired production of new $CD4^+$T-cells

This mechanism focuses on mature $CD4^+$T-cells, but these cells are often derived from early progenitors that may also express $CD4^+$T-cells. Such progenitors, include-ing multi-lineage and lineage-restricted haematopoietic progenitor cells are uniquely endowed with the capacity to persist with long half -lives and to generate large numbers of differentiated progeny rapidly upon stimu-lation. If these cells are destroyed or rendered non-functional, mature progeny could not be made (McCune, 2001; Hazenberg et al., 2003; Eggena et al., 2005). Evidence for suppression of multi- lineage and lineage-specific haematopoiesis has been available since the beginning of the AIDS epidemic (Pakker, 1998; Vajpayee et al., 2009).

Laboratory findings showed that when late-stage patients initially presented with opportunistic infections, they were not just lymphopenic, but anaemic, neutropenic and thrombocytopenic as well. These findings led to multiple diagnostic bone-marrow biopsies, the results of which were frequently abnormal. Microscopic examination revealed hypercellularity or hypocellularity, plasmacytosis, myeloid or erythroid dysplasia and a variety of other pathological changes (McCune and Kaneshima, 1995, Bialecki et al., 2009). Phenotypic and functional analysis of bone-marrow progenitor cells showed a decrease in the number of lineage-restricted colony-forming units and in some, but not all instances, infection and/or apoptotic death of $CD4^+$T-cell progenitors. Although the mechanisms associated with such cytopenias remain unclear, they are often reversed upon the provision of effective antiretroviral therapy (Fleury, 1998; Appay and Sauce, 2008).

The thymus, housing many $CD4^+$T-cells in varying stages of maturation, is another critical target organ for HIV infection. Examination of paediatric and adult specimens has revealed thymocyte depletion, loss of corticomedullary demarcation and development of thymic medullary B-cell follicles. These changes are associated with immunohistochemical visualization of structural proteins within thymocytes and are evidence of viral replication. Although it has proven difficult to study the thymus in HIV-infected humans, the frequency of circulating $CD4^+$ and $CD8^+$ naïve T-cells have been found to decrease as disease progresses (Roederer, 1995; Dandekar, 2007). In addition, cells bearing TCR excision circles also decrease in frequency with age and as a function of HIV disease progression (Zhang, 1998; Appay and Sauce, 2008). In return, signs of thymopoiesis return after treatment of some individuals with effective anti-retroviral therapy particularly if they are younger and have evidence of plenty thymocytes by computed tomography (Zhang, 1998). It has also been noticed that peripheral lymphoid organs undergo marked alterations after HIV infection. These changes include the accumulation of virus on and eventual destruction of the follicular dendritic cell network, decompartmentalisation and depletion of both the $CD4^+$ and $CD8^+$T - cell populations. Thus, HIV infection leads to profound disruption of the bone marrow, thymus and peripheral lymphoid organs and, where measurable, quantitative and qualitative defects in important $CD4^+$T progenitor cells (Roederer, 1995, Brenchley et al., 2004; Vajpayee et al., 2005; Appay and Sauce, 2008). With these cells eliminated or no longer functional, the immune system cannot be sustained.

Apoptotic signaling mechanism and activation by viral proteins

Viral load is seen as a good tool in monitoring disease progression in people living with HIV. Research reports have shown that there is a relationship between the extent of apoptosis and disease progression in HIV-infected persons. It is believed that one main pathway of T-cell apoptosis is mediated via the tumour necrosis factor family of receptors, particularly the Fas receptor (Cotton et al., 1997; Selliah and Finkel, 2001). Silvestris et al (1996) showed that peripheral blood lymphocytes from HIV-positive persons demonstrated higher Fas expression and that the proportion of Fas-expressing T-cells increases with disease progression. The viral protein Tat has been found to sensitize T-cells to T-cell receptor and CD4-induced apoptosis by up-regulation of FasL expression and to increase the sensitivity to Fas-mediated apoptosis by up-regulation of caspase-8. Also, Net has been shown to increase surface expression of both Fas and FasL and Net's capacity to interact with cellular kinases is required for this increased expression and for apoptosis (Bartz and Emerma, 1999; Zauli et al., 1999; Ondoa et al., 2005; Appay and Sauce, 2008). One

of the accessory HIV-1 proteins (Vpr) has been found to induce T-cell apoptosis as demonstrated by Jacotot et al. (2000). Jacotot and colleagues (2000) added synthetic viral protein R (Vpr) to intact T-cells and reported that Vpr caused a rapid dissipation of the mitochondrial transmembrane potential and the release of cytochrome c and cellular apoptosis. This finding support an earlier report (Macho et al., 1995; Wilson et al., 2004) that T-cells from HIV-positive persons have dysfunctional mitochondria reduced transmembrane potential and increased generation of superoxide anion.

It has been shown that only a small percentage (less than 0.1%) of $CD4^+$T-cells are productively infected and that the number of apoptotic $CD4^+$T- cells from the peripheral blood of HIV-positive persons is higher than the number of infected cells, which suggest that uninfected T-cells die by apoptosis (Carbonari et al., 1995; Dandekar, 2007). A cohort study of HIV-positive persons conducted by Gougeon et al. (1996) at different stages of HIV disease showed that the degree of apoptosis was significantly higher in $CD4^+$, $CD8^+$ and B-cells compared to HIV-negative persons and correlated with HIV disease progression. The study also reported low level of apoptosis in long-term non-progressors and a high level of apoptosis in fast progressors. Increased apoptosis has been reported in the lymph nodes of HIV-positive children and adult males and females. Apoptosis is known to occur in the absence of viral replication when infected and uninfected cells were cultured together indicating that viral proteins interact with uninfected cells and induce an apoptotic signal. The binding of HIV-1 Env to $CD4^+$ and CXCR4 (the chemokine receptor utilized by T-cell linetropic HIV) or CCR5 (the chemokine receptor utilized by macrophage- tropic HIV) has been shown to induce apoptosis in primary T lymphocytes (Pantaleo et al., 1993; Cicala et al., 2000; Dandekar, 2007).

Oxidative stress

The role of oxidative stress in the destruction of the immune cells have been elucidated (Repetto et al., 1996; Gil et al., 2003; Mates et al., 2000; Gil et al., 2005). Specifically, Mates et al. (2000) reported that the severe depletion of total antioxidant status in the AIDS stage of HIV infection indicated increase reactive oxygen species production which correlated with increased viral load and decreased $CD4^+$T-cell count. The center for disease control (CDC, 1992) also reported that low antioxidant status was significantly related to reduce $CD4^+$T-cell count. Laboratory- evidenced report shows that viral tat protein increased the apoptotic index by increasing production of intracellular reactive oxygen species. Antioxidants that are naturally endowed to protect the immune defence system are consumed and hence depleted in the process of protecting the cells against reactive oxygen species-induced oxidative damage. The depletion of these antioxidants (which include antioxidant enzymes such as catalase, superioxide dismutase, glutathione peroxidase, glutathione transferase, caeruloplasmin, vitamins such as vitamin A, E and C and minerals such as selenium and zinc) lead to the generation of more reactive oxygen species which consequently leads to immune depression and in turn further enhances HIV replication and further suppression of the of immune system/destruction of immune cells, followed by opportunistic infections as a result of depressed immune system and development of AIDS. In a study on HIV-positive/AIDS patients, Oguntibeju et al (2005; 2006) reported decreased dietary intake of antioxidants among the participants with a concomitant decrease in $CD4^+$T-cell count especially in those patients with $CD4^+$T-cell count <200 cells/mm^3.

$CD4^+$T-cell Count and prognosis

The $CD4^+$T-cell count has been shown in numerous clinical trials and natural history studies to be an independent risk factor for progression to AIDS and death. However, it has two major limitations: it is subject to considerable variation, for instance, inter-assay variability, diurnal variation, changes due to inter-current illness and thus it reflects existing damage to the immune system (Fauci et al., 1991; Mellors et al., 1995; Fox, 1996; Allen, 2000; Vajpayee et al., 2005; Vajpayee et al., 2009).

Opposing views on possible causes of $CD4^+$T-cell depletion

Various scientific investigators have reported on HIV replication, $CD4^+$T-cell depletion and the production of $CD4^+$T- cells by the immune system. Further investigations on HIV showed that HIV causes an increased rate of $CD4^+$T-cell proliferation and death and that antiretroviral therapy reduced viral replication and the rate of $CD4^+$T-cell death, resulting in an increase in the number of $CD4^+$T-cells (Kovacs, 2001). This view has raised scientific debates and many scientists are of the opinion that the gradual decrease in $CD4^+$T-cells is in part a consequence of the increased trapping of $CD4^+$T-cells in the lymph nodes as viral infection in these sites worsens with time. This trend has been observed in macaques infected with simian immunodeficiency virus (SIV) (Schenkel, 1999).

It is believed that the rapid rise in $CD4^+$Tcell counts within weeks following the administration of highly active antiretroviral therapy is a result of the shut-down of HIV replication in the lymph nodes, and the redistribution of $CD4^+$ T-cells back into blood circulation. It is said that $CD4^+$T-cell renewal could also be affected by damage to the bone marrow by destruction of precursor cell produc-

tion capacity by HIV, or by a direct effect of antiretroviral drugs, by interfering with $CD4^+$T-cell production in the thymus, or by interference with cell cycling and signaling (Mohri, 2001).

A research work opposing that of Ho et al. (1995) tap and drain model on HIV and $CD4^+$T-cell dynamics has been published (Hellerstein, 1999a). The author used a technique that was developed to label immune cells, and then studied the half-life and production rates of $CD4^+$T and $CD8^+$T-cells in nine HIV-negative people, seven untreated HIV-positive people, and five HIV-positive people who had undergone antiretroviral treatment for 12 weeks. In the untreated HIV-positive group, the half-life of each T -cell sub-population was found to be less than a third of that of the sero-negative controls. In contrast to Ho's proposed model, the investigator found that this reduced cell life span was not compensated for by increased cell production. Following viral suppression after twelve weeks of antiretroviral therapy, the investigator noted a significant increase in circulating $CD4^+$T and $CD8^+$ T-cells, but for $CD4^+$ T- cells, this was due to greater production rather than a longer half-life. The investigator concluded that the loss of $CD4^+$ T-cells that occurs in the course of HIV infection is not due to the exhaustion which follows a sustained over-production of cells, but instead to a shortened survival time and to a failure to increase the production of new $CD4^+$ T-cells (Hellerstein, 1999a).

This same investigator published a follow-up work in June of the same year showing that $CD4^+$T-cell survival time after twelve weeks and 18 months of antiretroviral therapy. It was reported that after 18 months of successful viral suppression, $CD4^+$ T-cell survival times had increased until they were almost equal to those seen in a healthy uninfected control group, from 14 to 78 days and production was elevated above normal levels during the first months of therapy but returned to normal or below average after 18 months (Hellerstein, 1999b).

Miedema (1998) has proposed that the key mechanism leading to loss of $CD4^+$T-cells is interference with the production of T-cell progenitors. These are produced in the bone marrow and migrate to the thymus where they are transformed into mature T-cells. In long-term non-progressors, Miedema (1998) reported that progenitor production is unchanged after six years of infection, whereas production declines in those with disease progression. According to Miedema (1998) antiretroviral therapy improves T-cell progenitor production and the improvement in naive $CD4^+$T-cell reconstitution seen on antiretroviral therapy correlates to the degree of improvement in progenitor production

A theory, proposed by Haynes Sheppard, is that $CD4^+$ T-cell depletion in HIV disease is a consequence of a confused immune system. According to Sheppard's model, the immune system mistakes HIV virions for $CD4^+$T-cells because HIV is able to mimic the $CD4^+$T-cell receptor, and so decreases the rate of $CD4^+$T-cell replacement in order to maintain a stable number of $CD4^+$T-cells.

Other researchers have also found that there is little difference in $CD4^+$T-cell turnover between HIV- negative and HIV-positive asymptomatic persons but that $CD8^+$ T-cells do turn over faster in HIV-positive persons than HIV-negative persons.

Conclusion

From this review it can be seen that based on experimental studies, different mechanisms combined to provide explanations for HIV- mediated depletion of $CD4^+$Tcells. These mechanisms range from accelerated destruction of matured $CD4^+$T-cells, chronic activation, oxidative stress to impaired production of $CD4^+$T-cells. The altered immune system leads to failure in signal network, followed by failure in the immune system to respond to invading organisms (imbalance between production and destruction of $CD4^+$T-cells) making HIV-infected persons to become vulnerable to opportunistic infections that typify AIDS. Further research is urgently needed that could possibly provide detail explanations into immune response in HIV-1 infection. Findings from such research studies could throw more light into the mechanisms involved in HIV-1 infection which could lead to the development of an effective vaccine against HIV.

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