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Role of Cytokines and Chemokines in HIV Infection

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1. Introduction

Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS). Blood monocytes and resident macrophages are important *in vivo* cell targets for HIV infection and their role in AIDS pathogenesis are well documented. These cells of innate immune defenses usually survive HIV infection, serve as a major virus reservoir, and function as immunoregulatory cells through secretion of several pro-inflammatory cytokines and chemokines in response to HIV infection, thereby recruiting and activating new target cells for the virus, including CD4+ T cells. This review describes the alterations in the synthesis of host cytokines and chemokines following HIV infection thereby favoring successful survival of the virus inside the host and enhancing the susceptibility of the host to opportunistic infections.

2. HIV and chemokine receptors

HIV infects immune cells of the macrophage and T-cell lineage. Entry into these cells requires CD4 as a receptor in addition to a co-receptor which most frequently is either chemokine receptor CCR5 or CXCR4 (Gorry & Ancuta, 2011). Binding and entry into human cells requires the two HIV envelope glycoproteins gp120 and gp41. Gp41 possesses a transmembrane domain and is associated with the viral envelope while Gp120 is present in association with Gp41 but does not insert into or contact the viral membrane (Tagliamonte *et al*; 2010). These two viral glycoproteins are present in HIV as tetramers. Therefore, three Gp41 molecules associate within the viral membrane, while three molecules of Gp120 associate with Gp41 (Tagliamonte *et al*; 2010). To facilitate HIV-1 entry into human cells, Gp120 binds to human cellular CD4 with high affinity. Binding causes a conformational change in Gp120 that reveals a co-receptor binding site. Binding to one of the chemokine

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receptors is then facilitated which in turn induces a conformational change in the glycoprotein gp41 N-terminus (Tagliamonte *et al*; 2010). A fusion peptide portion of gp41 inserts into the host cell membrane and lowers energy that is required for fusion of the host and viral membranes (Tagliamonte *et al*; 2010). The viral core is then translocated into the cytoplasm of the host cell.

HIV-1 viral variants can in general use either the CCR5 or CXCR4 co-receptor for entry into human cells (Gorry & Ancuta, 2011). They may also at times use a variety of other chemokine receptors for entry (Gorry *et al*; 2007). The normal function of chemokine receptors is to bind chemokines that target immune cells to areas of inflammation within the human body. Certain HIV-1 viruses may have an increased ability to either bind the CCR5 receptor and are known as R5 viruses, bind to CXCR4 and are known as X4 viruses, or bind with mixed affinity to either receptor. This differential affinity lies within the specific alterations in amino acid sequence of the gp120 glycoprotein (Gorry & Ancuta, 2011). Although not correlating completely, macrophage tropic HIV-1 viruses generally are R5 and T-cell tropic viruses are X4 viruses (Gorry & Ancuta, 2011). Early during infection R5 viruses predominate, and it appears that there is some mechanism which selects these viruses during the transmission process (Grivel *et al*; 2010). For example, an HIV-1 naive individual may be exposed to both R5 and X4 virus particles from an infected individual, but only become infected with the R5 viral particles. There may be multiple factors which affect this process, including co-receptor availability and pH at the sites of infection. Acidic pH may act to disrupt the cationic charge present in gp120 proteins which bind to CXCR4 preferentially (Kwong *et al*; 2010, Edo-Matas *et al*; 2010). R5 viruses are also prominent during chronic infection. X4 viruses or R5X4 viruses which have mixed affinity can arise later during infection and often their presence precedes disease progression and immune cell depletion (Mariani, 2010).

Deletion of the CCR5 receptor can in many cases abrogate infection with HIV-1 completely. It has previously been identified that individuals homozygous for a 32 base pair deletion within the *CCR5* gene resulting in a nonfunctional CCR5 molecule are resistant to infection with the HIV-1 virus, though there have been some instances where homozygous *CCR5Δ32* individuals were infected with X4 HIV-1 (Samson, 1996). Additionally, people who carry one allele of *CCR5Δ32* have a slower progression of the disease. This knowledge has led to the development of treatments for HIV-1 infection. Transplantation of stem cells from individuals homozygous for *CCR5Δ32* into CCR5 HIV-1 positive individuals resulted in clearing of the virus from the infected patients (Hutter, 2009). Monoclonal antibodies against CCR5 to inhibit binding of HIV-1 to this co-receptor are a potential therapeutic to prevent viral entry and replication (Tenorio, 2011, Suleiman, 2010). In addition there are plans to use an individual's native stem cells as a target to disrupt the *CCR5* receptor gene which can then be transplanted back into the HIV infected patient to effect elimination of the HIV-1 virus from the body (Cannon and June, 2011). Pitfalls of these therapies include the problem that the CCR5 chemokine receptor has a native function within the body, and that disrupting this receptor may cause unforeseen deficits in the immune system. In fact, lack of the CCR5 receptor gene has been associated with increased risk of severe infection with other viruses such as the West Nile Virus, and certain flaviviruses (Lin *et al*; 2008, Kindberg *et al*; 2008). Notwithstanding the previously mentioned caveat, interference with the CCR5 receptor may indeed be a promising target to treat those infected with HIV-1 as well as prevent infection for those exposed to the virus via sexual activity, needle sharing, or accidental hospital transmission.

3. Chemokine ligand-2 (CCL2)

CCL2 or monocyte chemotactic protein-1 (MCP-1), of the C-C chemokine family, is a cytokine with the ability to influence both innate and adaptive immune responses (Daly *et al*; 2003). This chemokine is produced by a variety of different cell types including endothelial cells, fibroblasts, epithelial cells, smooth muscle cells, mesangial cells, astrocytic cells, and microglial cells. However, despite the wide range of cell types that have the ability to manufacture CCL2, the majority of CCL2 is produced by macrophages and monocytes (Deshmane *et al*; 2009).

Although technically a chemokine, CCL2 is often classified as an inflammatory cytokine due to its ability to attract various leukocytes (monocytes, memory T cells, basophils, natural killer (NK) cells etc.) to sites of trauma, bacterial and mycobacterial infection, toxin exposure, and ischemia (Daly *et al*; 2003, Deshmane *et al*; 2009, Mahad *et al*; 2003,, Charo *et al*; 2006). Besides attracting various leukocytes, CCL2 also specifically regulates the infiltration of monocytes, memory T lymphocytes, and NK cells (Deshmane *et al*; 2009). In addition, CCL2 has been found to have a profound effect on the differentiation of naïve helper T cells (Daly *et al*; 2003). Interestingly, studies have found that CCL2 expression tends to lead to the development of a Th2 immune response. Taking this tendency into account, it seems likely that CCL2 concentrations in HIV patients, which Weiss *et al*. (Weiss *et al*; 1997) found were correlated with viral load, can be linked to the Th1 to Th2 cytokine response switch often observed in HIV-1-infected patients (Deshmane *et al*; 2009).

CCL2 has also been found to play other roles in HIV pathogenesis. Eugenin *et al.* (Eugenin *et al*; 2006) noted that CCL2 in the central nervous system (CNS) attracts HIV-infected leukocytes into the brain thereby increasing the rate of HIV-1-infected cell-dispersal and causing the eventual impairment of the blood-brain-barrier. In fact, multiple studies indicate that CCL2 is largely responsible for the development of HIV encephalitis (HIVE), HIV-1-associated dementia (HAD), and NeuroAIDS (Deshmane *et al*; 2009, Eugenin *et al*; 2006).

4. HIV and the Th1 to Th2 Cytokine shift

Under normal conditions, the immune system utilizes a Th1 subset response to viral infections. Activated antigen presenting cells (APC) secrete interleukin-12 (IL-12) which causes Th cell differentiation into the Th1 subset of cells (Clerci et al; 1993). These Th1 cells then secrete a characteristic Th1 profile of cytokines consisting of interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-beta (TNF-β). IL-2 induces proliferation of naïve Th cells (T_0), amplifying the Th response. IFN-γ induces further IL-12 production in activated APCs, amplifying the Th1 response, and suppressing any Th2 response. IFN-γ also plays an important role in the activation of cytotoxic T_C cells which destroy virally infected cells.

In individuals infected with HIV, the normal Th1 response to viral infection is shifted to a Th2 response (Klein et al; 1997, Osakwe et al; 2010). Measurement of the serum cytokine levels of HIV infected patients has revealed an increase in Th2 cytokines as well as a decrease in Th1 cytokines (Klein et al; 1997, Osakwe et al; 2010). Assays have shown elevated serum IL-4 levels in HIV seropositive individuals (Clerci et al; 1993). IL-4 in the presence of proliferating T_0 cells leads to their differentiation into the Th2 subset. Th2 cells promote B-cell proliferation, class switching, and eosinophil activation (Clerci et al; 1993). This Th2 response is not appropriate for control of intracellular pathogens such as HIV, and so allows it to persist and spread in $CD4^+$ T-cells.

5. TNF-α and HIV infection

It has also been shown that HIV infection induces increased production of TNF-α by macrophages. TNF-α stimulates the production of free radicals. Moreover, enhanced levels of free radicals are likely to increase TNF-α in various cells. TNF-α consists of 233 amino acids and is expressed on all somatic cells, particularly on the cell membrane where it becomes hydrolyzed to its soluble form. TNF-α is considered as one of the most highly studied pro-inflammatory cytokines because it plays a critical role in the origin and progression of diseases such as HIV-1 (Bahia and Silakari, 2010). The immuno-regulatory response of the host influences the pathogenesis of HIV-1 infection, triggering monocytes, macrophages, and natural killer cells to produce TNF-α (Alfano and Poli, 2005). As a result, there is a positive correlation between HIV-1 viremia and TNF-α levels in serum of HIV-1 infected patients. This relationship suggests that reducing TNF-α levels may also reduce occurrence of HIV-1 viremia. In excess, TNF-α may cause severe inflammatory damage and toxicity, making control of its production and secretion highly important. Regulating its release serves as a potential means of therapy for HIV-1 and other diseases. TNF-α can also induce other pro-inflammatory cytokines such as IL-6 and IL-8, which aid in the upregulation of viral replication (Fernandez-Ortega et al; 2004). Studies have also shown the ability of TNF-α to stimulate production of anti-inflammatory cytokine IL-10, preventing further inflammation by causing TNF-α inhibition (Leghmari et al; 2008). TNF-α is secreted during the early phase of acute inflammatory diseases. Its pathogenic role in HIV-1 infection involves activation of nuclear factor kB (NF-κB), stimulating apoptosis of T lymphocytes. Tissue and plasma samples of hosts express high levels of TNF-α, contributing to fever, anorexia, and other symptoms of HIV/AIDS. TNF-α must be targeted at an appropriate time during production to prevent progression to the chronic stage. Local effect of the cytokine may be beneficial to the host, so monitoring its development is critical. Highly active antiretroviral therapy helps to reduce mortality rates, and development of potent antiretroviral drugs blocking HIV transcription continues to be successful. However, drug resistance and toxicity remains a challenge in this field of medicine (Fernandez-Ortega et al; 2004).

6. Interleukin 1 (IL-1) and HIV infection

HIV infection and its viral proteins can disturb the production of cytokines and disrupt their usual interactions resulting in disruption of the normal immune function. IL-1 and TNF-α are produced by activation of mononuclear phagocytes as well as microglia in the brain in response to normal immune stimuli such as immune complexes, lipopolysaccharides and phorbol esters (Burchett et al; 1998). It has been reported that IL-1 and TNF-α will be produced by either the binding of gp120 to the CD4 molecules on mononuclear phagocytes or infection with HIV (Merrill et al; 1989, Cheung et al; 2008).

IL-1 is the first discovered and most studied member of the cytokine family (Fantuzzi, 2003). IL-1 is a pro-inflammatory cytokine that plays a fundamental role in host defense by inducing acute and chronic inflammation through activation of the innate and acquired immune systems (Nambu and Nakae, 2010). IL-1 has been described as the prototypic pro-inflammatory cytokine as it was originally described as the first "endogenous" pyrogen due to its fever-inducing properties in both rabbits and humans (Dinarello, 1999). However, in spite of much research in the area of fever induction, the role of IL-1 in this area is still

undefined (Fantuzzi, 2003). IL-1 consists of two distinct ligands (IL-1α and IL-1β) with two indistinguishable biological activities that signal through the IL-1 receptor (IL-1R1) (Bujak and Frangogiannis, 2009). Both IL-1α and IL-1β can also bind the IL-1 receptor accessory protein (IL-1RAcP). Once bound to the receptor, the complex transduces a signal that initiates a wide variety of inflammatory genes by activating the NF-κB system. The NF-κB transcribed genes can produce a variety of inflammatory products including chemokines, pro-inflammatory cytokines, such as TNF-α, IL-6 or IL-8 (Nambu and Nakae, 2010), adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) (Marui et al; 1993), colony-stimulating factors, and mesenchymal growth factor genes (Bujak and Frangogiannis, 2009). In addition, expression of inducible nitric oxide synthase, type 2 cyclooxygenase (COX)-2, and type 2 phospholipase A_2 is exquisitely sensitive to IL-1 (Bujak and Frangogiannis, 2009). IL-1 has also been associated with augmentation of the mast cell activation and Th2 cytokine secretion, suggesting involvement of IL-1 in allergic diseases such as allergic asthma (Dinarello, 1999).

Knockouts of IL-1 have been used to study acute and chronic neurodegenerative conditions, in which a role for IL-1 has been well established (Fantuzzi, 2003). For example, in rodent studies the presence of IL-1 after occlusion of the middle cerebral artery will increase the ischemic damage area. It has been shown that caspase-1 cleaves the inactive pre-form to the active mature form of IL-1β, which contributes to the damage from ischemia (Bujak and Frangogiannis, 2009). In resting cells, procaspase-1 is bound to an inhibitory molecule that prevents its activation. After damage to cells, conversion of procaspase-1 to caspase-1 is triggered by a molecular complex termed the "IL-1β inflammasome" (Martinon, 2002).

Macrophages and dendritic cells produce IL-1, IL-12 and other cytokines that permit CD4 cells to reach the level of maturation needed to produce IL-2, which is needed for self-replication of the CD4 cells and for the growth and function of CD8 cells (Levy, 2007). Thus IL-1 plays a role in maintaining normal immune function.

Elevation of IL-1 and TNF-α has been demonstrated in the serum of some patients with HIV-1 (Lepe-Zuniga et al; 1987). High levels of IL-1 (Lepe-Zuniga et al; 1987, Weiss et al; 1989, Molina et al; 1989, Roux-Lombard et al; 1989, Emilie et al; 1990) and TNF-α (Roux-Lombard et al; 1989) are produced in the supernatant of cultured peripheral blood monocyte early in the onset of HIV disease. The levels of TNF-α and IL-1 in the serum were positively correlated in symptomatic versus asymptomatic individuals (Lepe-Zuniga et al; 1987). HIV virus is present in mononuclear phagocytes and in the blood and brain of AIDS patients. Production of IL-1 and TNF-α from mononuclear phagocytes after stimulation with HIV-1 may contribute to some of the symptoms of AIDS such as fever, cachexia and aseptic meningitis (Merrill et al; 1989).

Chronic infection and viral latency are typical of HIV-1 infection. Stimulation with IL-1β as well as TNF-α can stimulate viral replication in chronically infected cells (Devadas et al; 2004). Monocytes are also major reservoirs for HIV-1 in infected tissue and vectors for virus transmission to target cells, as well as sources of potent cytokines that can affect cell function and virus replication (Devadas et al; 2004). It is thought that stimulation of viral replication in chronically infected cells is due to activation of NF-κB. In addition to IL-1 and TNF-α, contact with macrophages as well as a number of stressors can stimulate NF-κB, including phorbol esters, radical oxygen intermediates, and UV irradiation (Devadas et al; 2004).

Clinical manifestations of AIDS include both immunologic and neurologic disorders. In the brain it has been shown that IL-1 induces activation and proliferation of astrocytes, while TNF-α contributes to necrosis of cerebral blood vessels and possibly to demyelination

(Merrill et al; 1989). A feedback process has been described in which HIV-1 and TNF-α can each induce expression of the other. It has been proposed that IL-1 will participate in this feedback loop by inducing TNF-α or by direct T-cell activation, which is needed for HIV-1 replication (Merrill et al; 1989).

IL-1 has been implicated in the pathogenesis of HIV associated dementia (HAD) (Kaul et al; 2001). Both IL-1β and TNF-α are highly expressed in the central nervous system (CNS) of individuals with HAD, correlate with neuronal injury and are implicated in the pathogenesis of HAD (Epstein and Gendelman, 1993,, Brabers and Nottet, 2006). HIV-1, recombinant gp120, and viral transactivator Tat can activate astrocytes to secrete pro-inflammatory cytokines TNF-α, IL-6, and IL-1β (Corasaniti et al; 2001), which may contribute to the inflammatory environment in the brain (Herbein and Varin, 2010). Microglia and macrophages in the brain can release IL-1β after stimulation with HIV-1 envelope protein gp120 (Merrill et al; 1992, Wahl et al; 1989), which is elevated in brain during HIV (Tyor et al; 1992) and has been shown to be elevated in the cerebral spinal fluid during HIV infection (Gallo et al; 1989).

About 25% of subjects with HIV will develop dementia, particularly HIV encephalitis (HIVE), which can occur in spite of the use of HAART (Levy, 2007). Macrophage inflammatory products including IL-1β have been demonstrated in HIV related encephalitis in mouse and human brain tissue (Persidsky et al; 1997). It has been suggested that the release of neurotoxins, including L-cysteine, from macrophages in the brain is mediated by IL-1 following stimulation of the macrophages by the HIV membrane protein gp120.

L-Cysteine can be released from human monocyte derived macrophages stimulated by either gp120 (Lipton, 1998), or by IL-1 (Yeh et al; 2000). It has been suggested that cytokines including IL-1 may mediate the neurotoxic actions of gp120 (Yeh et al; 2000). Cysteine can act as an endogenous neurotoxin (Olney et al; 1990), which under both physiologic and pathophysiologic conditions stimulates *N*-methyl-D-aspartate subtype of glutamate receptor (NMDARs) and leads to neuronal apoptosis (Yeh et al; 2000). Thus, immune activation of macrophages in the brain without direct HIV infection may lead to neural damage (Yeh et al; 2000).

Autopsy evaluation of brain tissue from HIVE cases shows increased IL-1β in the frontal white matter of all 11 of the brains evaluated (67). Additionally, IL-1β, but not TNF-α expression was detected in HIVp24-positive cells in the HIVE patients, which indicates that IL-1β is induced by HIV-1 infection. The authors concluded that a macrophage/microglia lineage is the main cell type to release cytokines in HIVE, and IL-1β expression by HIV-1-infected cells may be one of the important factors for induction of HIVE (67).

7. Interleukin-6 (IL-6)

The family of IL-6-type cytokines comprises IL-6, IL-11, LIF (leukaemia inhibitory factor), OSM (oncostatin M), CNTF (ciliary neurotrophic factor), CT-1 (cardiotrophin-1) and CLC (cardiotrophin-like cytokine) (Heinrich et al; 2003). IL-6 is a pleiotropic cytokine that is commonly produced at local tissue sites and released into circulation in almost all situations of homeostatic perturbation typically including endotoxemia, endotoxic lung, trauma, and acute infections. In addition to its critical participation in the generation of immunity against chronic intracellular infections, circulating IL-6, together with other alarm cytokines TNF-α and IL-1, is known to be required for the induction of acute phase reactions composed of fever, corticosterone release, and hepatic production of acute phase proteins many of which

are protease inhibitors (Xing et al; 1998). They activate target genes involved in differentiation, survival, apoptosis and proliferation. The members of this cytokine family have pro- as well as anti-inflammatory properties and are major players in haematopoiesis, as well as in acute-phase and immune responses of the organism. IL-6-type cytokines bind to plasma membrane receptor complexes containing the common signal transducing receptor chain gp 130 (glycoprotein 130). Signal transduction involves the activation of JAK (Janus kinase) tyrosine kinase family members, leading to the activation of transcription factors of the STAT (signal transducers and activators of transcription) family. Another major signaling pathway for IL-6-type cytokines is the MAPK (mitogen-activated protein kinase) cascade (Heinrich et al; 2003). IL-6 was originally identified as β2 (IFN-β2), IL-1-inducible 26kD protein and as a factor that induces the differentiation of B cells to antibody producing plasma cells (Hibi et al; 1996).

The induction of IL-6 by live HIV preparations occurred in the absence of T cells and could be neutralized by human anti-HIV serum indicating that HIV was responsible for this IL-6 inducing activity. It has been demonstrated that IL-6 can be produced by a variety of cells upon various kinds of stimulation: T cells infected with HTLV-1, fibroblasts stimulated with polyI:C, IL-1, platelet-derived growth factor, TNF-α, FCS, or LPS, and monocyte/macrophages stimulated with LPS. Monocyte/ macrophages, one of the target cells of HIV, produced IL-6 upon stimulation with both live and inactivated HIV (Nakajima et al; 1989). A study of women treated for cervical intraepithelial lesions showed that after treatment, there were increased levels of genital HIV, TNF-α, IL-6, and other activation markers in cervicovaginal lavage (Spear et al; 2008). In univariate analysis, genital tract HIV RNA was significantly associated with plasma HIV RNA and several of the cytokines, while in multivariate analysis, genital tract HIV RNA was significantly associated only with plasma HIV RNA and IL-6 (Spear et al; 2008). Another study was done to determine the effect of HIV on thymic stromal cells and the production of cytokines important in thymocyte development, three types of adherent thymic cultures were established and studied: thymic epithelial cells (TECs), macrophage-enriched, and mixed cultures of macrophages and TECs (M phi/TEC). M phi/TEC and macrophage-enriched cultures were infected by both HIV strains without cytopathic changes. The TECs grew well in culture exposed to HIV-1 strains HIV-1IIIB and HIV-1Ba-L for at least 6 weeks and showed no evidence of infection, cytopathology, or changes in cytokine production with HIV. Only cultures containing macrophages (M phi/TEC or macrophage enriched) showed changes in cytokine (IL-1 alpha, IL-1 beta, and IL-6) production with HIV. Unstimulated macrophage-enriched cultures produced small amounts of IL-6 that were increased by HIV 20-fold (Sandborg et al; 1994).

There are many studies showing the increase of IL-6 expression within HIV infected cells but not many studies suggesting what IL-6 does to HIV. In a study done by Miles in 1990, it was found that IL-6 might actually be a growth factor for the HIV virus (Miles et al; 1990). There was a proliferative response of the AIDS-Kaposi sarcoma (AIDS-KS) cells to high concentrations of hrIL-6 and the detection of IL-6-rRNA in the areas of the skin involved with Kaposi sarcoma. AIDS-KS cells synthesized, released, and responded to biologically active IL-6. AIDS-KS cells, in which IL-6 protein translation arrest was induced by an IL-6 anti sense oligodeoxynucleotide, did not proliferate optimally unless exogenous hrIL-6 was added (Miles et al; 1990).

8. Interleukin-17 (IL-17)

IL-17 is an inflammatory cytokine that is exclusively produced by a recently discovered subset of CD4+ T helper (Th) cells, referred to as Th17 cells (Crome et al; 2009). This cytokine has been found to help regulate the inflammatory response by activating fibroblasts, recruiting neutrophils, and acting on macrophages to promote both their recruitment and survival (Crome et al; 2009, Chang et al; 2007). In addition, IL-17 is thought to play a significant role in activating and inducing anti-microbial peptides and pro-inflammatory cytokines like IL-6, CCL2, and TNF-α (Crome et al; 2009, Chang et al; 2007). Furthermore, high levels of this cytokine have been linked to a number of inflammatory diseases including rheumatoid arthritis, multiple sclerosis (MS), and asthma. Low levels, on the other hand, are thought to cause both impaired host defense against mycobacterial infection and decreased antibacterial immunity (Crome et al; 2009, Brenchley et al; 2008).

Studies of the effects of HIV on IL-17 concentrations using flow cytometry have found that HIV-infected patients have significantly increased levels of IL-17 (Giorgio, 2003). Venketaraman *et al.* (unpublished data) was also able to show increased levels of IL-17 in HIV-infected blood plasma using ELISA assays. However, Brenchley *et al.*; 2008 noted that there were significantly fewer IL-17 producing Th17 cells in the gastrointestinal tract of HIV-infected patients. In fact, the study indicated that Th17 cells were preferentially targeted during HIV infection.

The decrease of IL-17 concentrations at the mucosal wall of the gastrointestinal tract could greatly increase the probability of bacterial infections, which could in turn have significant implications for the speed of HIV pathogenesis (Brenchley et al; 2008). As Levy et al; 2009 noted, chronic immune activation increases the production of pro-inflammatory cytokines (IL-6, IL-17, TNF-α, etc.). This up-regulation of pro-inflammatory cytokines often leads to the rapid loss of CD4+ T cells via apoptosis. Decreased IL-17 concentrations due to HIV infection can therefore ultimately lead to the general advancement of HIV by creating an environment favorable to opportunistic infection and chronic immune activation (Maek-A-Nantawat et al; 2007).

9. Interleukin-12 (IL-12)

IL-12 is a heterodimeric pro-inflammatory cytokine that is produced by dendritic cells and phagocytes during an infection (Giorgio, 2003). It is a cytokine identified as a master switch for leading the naïve CD4+ T cells towards the Th1 pathway and also activating NK cells (Villinger and Ansari, 2010). Not only does it directly induce T, NK, and NKT cell cytotoxicity, IL-12 also promotes macrophage activity via T- and NK-cell-produced IFN-γ (Giorgio, 2003, Egilmez et al; 2011). The pathway is antagonized in the presence of IL-10 (Villinger and Ansari, 2010).

IL-12 plays important roles in protecting the body from various microbial infections such as parasites, bacteria, and viruses (Yang et al; 2010). With mutations in genes of the IL-12, the cells are susceptible to intracellular pathogens such as tuberculosis, leprosy, HIV-1, hepatitis and malaria (Vannberg et al; 2011). One of the characteristics of HIV infection is the gradual deterioration of cellular effector responses. Studies has concluded that CD4+ and CD8+ T cell responses were enhanced *ex vivo* by the addition of IL-12, but that capacity to respond is decreased in patients with marked CD4 loss (Villinger and Ansari, 2010). Louis *et al;*. 2010, also added that IL-12 production required the presence of IFN-γ. Therefore, as HIV

progresses, decreased IFN-γ leads to decrease in IL-12 which leads to decreased CD4+ and CD8+ T cell response.
A decrease of IL-12 concentration increases the probability for opportunistic infections. Taoufik *et al*; 1997 and Mirani *et al*; 2002, showed IL-12 mRNA was diminished while IL-10 production was up-regulated in the presence of *Staphylococcus aureus* and HIV gp120, further inhibiting IL-12 cytokine production. Even though IL-12 is potent, Villinger and Ansari 2010, noted that when IL-12 therapy was administered in the late stages of HIV, it failed to restore normal levels of CD4 T cells and IFN-γ.

10. Additional effects of HIV on IFN-γ signaling

In addition to the Th1 subset response mediation mentioned earlier, IFN-γ normally acts on APCs to enhance their expression of major histocompatibility complex II (MHC-II), thereby enhancing their antigen presentation ability (Li et al; 2011). HIV transactivator protein (TAT) interferes with the intracellular signaling normally performed by the IFN-γ bound IFN-γ receptor (Cheng et al; 2009). In so doing, the TAT protein lowers the antigen presentation capacity of dendritic cells and macrophages, further limiting the immune response to the invading virus (Salgame et al; 2009).

11. The transforming growth factor β (TGF-β)

TGF-β cytokine family are closely related polypeptides which include tissue growth factors that have a diverse range of proteins that regulate many physiological processes including embryonic development, homeostasis, wound healing, chemotaxis, cell cycle control, cell proliferation, differentiation, apoptosis, adhesion, and migration (Leask and Abraham, 2004). TGF-β is one of the most immunosuppressive substances produced in the body and yet may inhibit or stimulate cell growth, depending on the cell type and culture conditions (Liu and Gaston Pravia, 2010). TGF-β is produced in many immune cells including lymphocytes, macrophages and dendritic cells (Liu and Gaston Pravia, 2010). Receptors for TGF-β have been found on all cell lines tested, allowing this cytokine to have effects on almost any tissue in the body (Leask and Abraham, 2004). It has also been shown to play a central role in tissue fibrosis (Leask and Abraham, 2004). Because of the multifunctional role played by TGF-β, it plays a central role in the pathogenesis of many diseases.(Leask and Abraham, 2004).
There are three forms of TGF-β (TGF-β1, TGF-β2, and TGF-β3) in mammalian cells. TGF-βs are synthesized using inactive precursors and cannot bind receptors until they are activated. After release of TGF-β from cells they associate with latency-associated protein and form a small inactive complex. In the extracellular matrix, this complex is bound by latent TGF-β-binding protein (LTBP), a component of the extracellular matrix that is necessary for the secretion and storage of TGF-β (Letterio and Roberts, 1998). Intracellular activity of TGF-β is mediated by the actions of Smad transcription factors as well as independent factors (Letterio and Roberts, 1998). Active Smad complexes bind to DNA weakly and high affinity binding is achieved by the association of Smad proteins with a large number of transcription factor partners (Massague, 1992). The variations of Smad proteins in transcriptional regulations and the diversity of Smad-independent pathways allow the pleiotropic actions of TGF-β (Letterio and Roberts, 1998).

HIV infection leads to a variety of disturbances in cytokine expression that can lead to a state of chronic activation of B cells and release of cytokines that may actually play an important role in the pathogenesis of HIV infection (Li and Flavell, 2008). Early HIV-1 infection is associated with a massive oligoclonal expansion of CD8 T cells (Massague and Gomis, 2006), however despite the high number of circulating CD8+ T cells the cytotoxic T lymphocyte (CTL) response is highly variable among HIV-1 infected individuals (Poli and Fauci, 1993). It has also been shown that the immune dysfunction in the initial phase of HIV infection exceeds CD4+ T cell infection and loss (Pantaleo et al; 1994). It appears that the immunosuppression effect occurs almost immediately upon infection (Garba et al; 2002). The result is diminished T cell response to antigen stimulation and persistence of HIV replication (Pantaleo and Fauci, 1995).

HIV-1 products such as TAT, induce the transcription of cytokines with immunosuppressive effects, including TGF-β (Cohen et al; 1999). It has been reported that extracellular TAT can be taken up by bystander cells and that it is possible that exogenous TAT, not associated with direct infection of a cell, can induce TGF-β transcription in immune competent cells (Pantaleo et al; 1993). Macrophages appear to be very sensitive to TAT and are affected by TAT concentrations 1,000-fold lower (500 pM) than those that affect T cells (Cohen et al; 1999). Macrophages stimulated by TAT either by infection or by the uptake of soluble TAT (sTat) induce Fas ligand (FasL), which in turn can trigger the apoptosis of antigen-reacting, Fas-expressing helper T cells. This mechanism would suppress T-cell dependent cellular and humoral immune responses to both HIV and other antigens (Cohen et al; 1999).

The transactivating effect of HIV-1 TAT is mediated by activator protein-1, which is the same multimolecular complex that is activated by TGF-β (Cohen et al; 1999). HIV-1 can induce both the transcription and secretion of TGF-β (Reinhold et al; 1999) and the induction of TGF-β can increase the apoptosis of NK cells (Poggi and Zocchi, 2006). TGF-β and Tat have been detected in the sera of early HIV-1 infected individuals at levels that were biologically active *in vitro* (Reinhold et al; 1999).

Some HIV-infected individuals have been shown to lose the ability of their cytotoxic T lymphocytes CTL ($CD8^+$) to control infection in cells that carry HIV as well as other infectious agents (Pantaleo et al; 1993). About 25% of HIV infected individuals have been shown to produce TGF-β1 in response to stimulation with HIV proteins or peptides (Garba et al; 2002). It has been shown that the loss of CTL activity is related to the production of TGF-β1 in sufficient amounts to significantly reduce the IFN-γ response of $CD8^+$ cells to both HIV and other viral proteins such as vaccinia virus (Garba et al; 2002).

It has been established that feline $CD4^+CD25^+$ T regulatory (T reg) cells share phenotypic and functional characteristics with human and murine T reg cells (Vahlenkamp et al; 2004). Early in the infection with feline immunodeficiency virus (FIV), $CD4^+CD25^+$ T reg cells exhibit increased expression of a membrane TGF- β (mTGF-β) (Mexas et al; 2008). The appearance of TGF-$\beta^+CD4^+CD25^+$ lymphocytes within the lymph node of FIV^+ cats occurs in both acute and chronic FIV, even though mTGF-β does not appear in the blood (Fogle et al; 2010). There is also evidence of increased expression of TGF-βRII, the receptor of TGF-β1, on $CD8^+$ lymphocytes in FIV^+ cats that would make the $CD8^+$ lymphocytes much more sensitive to TGF-β inhibition (Fogle et al; 2010). In FIV lentiviral infection, during both the acute and chronic stages of infection, $CD4^+CD25^+$ Tregs suppress $CD8^+$ responses and the $CD4^+CD25^+$ Tregs use mTGF-β to suppress IFN-γ expression resulting in suppression of $CD8^+$ lymphocyte function (Fogle et al; 2010). These findings help explain the paradox of chronic HIV-1 infection, in which $CD8^+$ T cells display an activated phenotype but exhibit

reduced effector function (Fogle et al; 2010, Bucci et al; 1998, Tompkins and Tompkins 2008). IL-10 and TGF-β overlap with each other in many of their biological effects including inhibition of T cell proliferation and IFN-γ production (Othieno et al; 1999).

12. Interleukin-10 (IL-10)

IL-10 is an anti-inflammatory cytokine that essentially plays two regulatory roles in innate and adaptive immunity. It suppresses the up-regulation of various genes in macrophages and dendritic cells that are normally stimulated via toll-like receptors and promotes the proliferation of cytotoxic T cells, activates B cells, and induces the upregulation of specific genes in toll-like receptor activated phagocytic and dendritic cells (Trincheri, 2007). In addition, a critical function of IL-10 is its ability to inhibit pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1, IL-6, IL-2, and IL-12 (Trincheri, 2007). IL-10 decreases the production of pro-inflammatory cytokines by limiting the major histocompatibility class II and CD80/CD 86 expressed on monocytes and macrophage (Wang et al; 2005). IL-10 was believed to be produced by CD4+ Th2 cells; however, studies have shown that it is secreted by both Th1 and Th2 cells (Brockman et al; 2009). Also, cells from the myeloid lineage which include macrophages and dendritic cells also produce cytokine IL-10 (Hedrich and Bream, 2010). Furthermore, IL-10 is regulated both at the transcriptional and post-translational level and is involved in various signaling pathways (Couper et al; 2008).

There are several speculations of the role of IL-10 in HIV pathogenesis and the subject has been a popular interest in many studies. Ji *et al*., 2005 reported that CD14+ monocytes are the main cells producing cytokine IL-10 in PBMCs after HIV-1 infection via interactions independent of CD4+ molecules, thus, concluding that IL-10 production is dependent on the presence of CD14+ monocytes. Moreover, as the patient progresses to advanced stages of HIV disease, the frequency of IL-10 producing cells increases significantly (118). On the other hand, Naicker *et al*., 2009, stated that different stages of the HIV disease will govern what role IL-10 will play in infected individuals. For instance, in acute HIV-1 individuals, IL-10 may promote viral replication by inhibiting effector immune response from both arms of the innate and adaptive immunity (Naicker et al; 2009). Furthermore, it was proposed in a chronic phase, that IL-10 resembled a protective role by reducing immune activation, inhibiting virus replication in macrophages, and the increase in production of IL-10 levels lowered plasma viral load and increased CD4+ cell count (Naicker et al; 2009).

13. HIV and free radicals

It has been shown that HIV infection induces increased production of free radicals by macrophages. Free radical formation occurs as a byproduct of oxidative stress. Oxidative stress occurs when there is a disproportion between the reactive oxygen elements in the body versus the ability of the body to properly eliminate these reactive species. The presence of free radicals has been implicated in disturbing and damaging a number of biological processes (Karthikeyan et al; 2010). With regards to HIV infection the increase of oxidative stress has been seen to influence components in antioxidant defense in physiological antioxidants such as glutathione which are seen to decrease dramatically in HIV patients (Pace and Leaf, 1995). In addition to glutathione, vitamin A, C, and E at high doses as well as improving low levels of selenium were associated with assisting the prevention of HIV infection progression by working as antioxidants to remove free radicals

(Garland and Fawzi, 1999). The aforementioned studies may provide a low cost method for improving the prognosis of HIV infected patients in high risk, underprivileged areas of the world.

Chronic oxidative stress is often associated with HIV infection and research indicates a benefit for increased antioxidant vitamins and supplements in reduction of DNA base damage, which in turn can slow progression of infection (Jaruga et al; 2002). Neutrophils from asymptomatic HIV patients show increased oxygen radical production which can be modified by treating with N-acetyl cysteine, a compound used as an antioxidant (Smietana et al; 2008). The role of free radical oxidative stress on DNA damage is correlated with stimulated DNA repair mechanisms which activate enzymes associated with initiation of apoptosis such as poly ADP-ribose transferase and p53. Reduced NAD/NADH production would lower ATP synthesis that in turn correlates with a deficiency in glutathione; which as mentioned is an endogenous antioxidant important in resolving imbalance of free radicals (Dobmeyer et al; 1997).

The progression of HIV is correlated with a decreased immunity. One way in which this decreased immunity progresses is by free radical overload of monocytes and granulocytes which leads to deficiency of antioxidant mechanisms which may lead to the loss of CD4 cells often seen in the progression of HIV (Dobmeyer et al; 1997). The decreased immunity may also be related to the reactive oxygen species and free radical presence which is higher in HIV infected patients. With HIV infection progression there is an increased production of reactive oxygen species which leads to the theory of free radical mediated apoptosis of lymphocytes which reduces the ability for immune response to progressive HIV infections (Dobmeyer et al; 1997). With regards to CD4 cell counts the apoptosis of lymphocytes by free radicals leads to progression of immunodeficiency and makes for a quicker transition from HIV infection to AIDS (Bautisita, 2001). It has been published that during HIV-1 infection, hematopoietic cells are exposed to high amounts of free radicals. Subsequently there is a reduction of leukocytopoiesis and increase susceptibility to further infections (Masutani, 2000). Furthermore, there is a link to lipid peroxidation observed in patients with HIV or AIDS to a deficiency of antioxidants which leads to free radical proliferation (Favier et al; 1994).

Rate of viral replication is a key process to the proliferation of HIV infection. The conditions in which viruses such as HIV will proliferate seem to correlate with the presence of oxidative stress/free radicals *in vitro* (Fuchs et al; 1991). There tends to be an increase in nuclear transcription factor and inflammatory cytokine activation of the immune system (Brach et al; 1992). The progression of the virus/infection will then allow for opportunistic infections which then would also promote more oxidative stress due to increased free radical elements, again improving viral replication and weakening antioxidant defense (Knysz, 2007).

Damage or altering of the DNA repair machinery is an important aspect of the progression of HIV infection pathogenesis (Olinski et al; 2002). There is a slow and deliberate degradation of cellular components such as membrane blebbing, chromatin condensation, and DNA cleavage ability. Additionally, there is evidence that shows oxidative DNA damage will lead to the apoptotic cell death in HIV infected patients. There appears to be an increase in oxidatively modified DNA bases in HIV infected patients leading to what is known as pyrimidine and purine derived lesions. One specific lesion labeled, 8-OH-Gua was found in isolated lymphocytes of HIV patients. The presence of this lesion leads to transversions of DNA base pairs unless repaired before replication. The number of these

lesions was seen to be reduced in response to antioxidant supplement and vitamin treatments, which correlates to free radical influence in DNA damage, and potential progression of HIV infection (Olinski et al; 2002).

14. Conclusion

Both HIV-1 and HIV-2 cause AIDS, but HIV-1 is found worldwide, whereas HIV-2 is found primarily in West Africa. Chemokine receptors, such as CXCR4 and CCR5 proteins, are required for the entry of HIV into CD4-positive cells. After establishing infection, HIV alters the synthesis of host cytokines and chemokines and kills CD4+ T lymphocytes thereby resulting in the loss of cell-mediated immunity and a high probability that the host will develop opportunistic infections.

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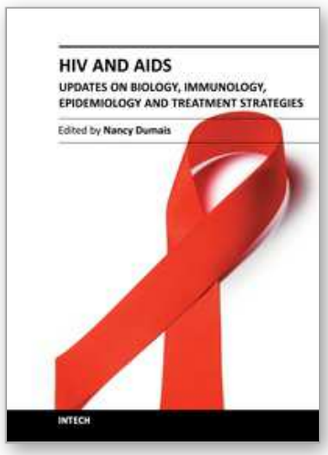

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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, â€œFrom the laboratory to the clinic,â€ and the second part, â€œFrom the clinic to the patients,â€ represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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