Chapter I

Introduction

Acquired immunodeficiency syndrome (AIDS) is the advanced stage of human immunodeficiency virus type 1 or 2 (HIV -1 , HIV-2) infection. Acute infection with HIV, which may present with mononucleosis - like symptoms, is followed by an asymptomatic period of a few months to more than 13 years. This asymptomatic period is characterized by declining numbers of circulating CD4 + T cells, and eventually leads to immunodeficiency and clinical of AIDS. The consequences of this include lymphadenopathy, infections with opportunistic pathogens, neoplasm such as Kaposi's sarcoma, and dementia. The opportunistic infections are mainly caused by intracellular pathogens like viruses, mycobacteria, protozoa , and fungi , which are indicative of failing cellular immunity (1).

Although the steady decline in CD4 + cells is associated with progressive HIV disease and low CD4 + cell counts are predictive of increase risk of disease progression (2), the state of disease also correlates with the depressed functions of macrophages such as faulty chemotaxis, reduced microbicidal properties and reduced expression of some inflammatory proteins (3). Lipopolysaccharide (LPS) -stimulated tissue factor (TF) mRNA has been shown to decrease in monocytes from individuals with symptomatic HIV infection (4). The observation of the selective reduction in induced TF expression was paralleled by decreases in delayed typed hypersensitivity (DTH) responses to test antigens in patients with AIDS and AIDS related complex (ARC) (4,5). TNF-α and IL-1β are differentially up-regulated in unstimulated monocytes during asymptomatic stage of HIV infection and with a loss of up-regulation in symptomatic individuals (4). These proinflammatory cytokines also induce HIV viral replication by the cellular nuclear factor kappa B (κB) via 5$'$ long terminal repeat of HIV proviral DNA (6,7). Activated macrophages produce IL-12 that plays a critical role in T helper (Th) - 1 cell differentiation. HIV-1-infected individuals have impaired IL-12 p40 and p70 production in their peripheral blood mononuclear cells (PBMC) upon stimulation with *S. aureus* antigen (8).

Interleukin 18 (IL-18), originally called interferon (IFN) - γ -inducing factor (IGIF), is a recently cloned proinflammatory cytokine of approximately 18 kDa. It is synthesized by Kupffer cells and activated macrophages (9,10). The major activity associated with this molecule is the induction of IFN-γ production from anti -CD3-activated Th1 cells in the presence of IL-12 (11). Study of IL-18 expression by reverse transcription - polymerase chain reaction (RT-PCR) revealed that human PBMC could express IL-18 transcript regardless of stimulation and did not significantly increase expression by phytohemagglutinin (PHA) or lipopolysaccharide (LPS) induction (12). *In vitro*, IL-18 has been shown to enhance HIV replication in a monocytic cell line (13). Nonetheless, the roles of IL-18 in HIV infection *in vitro* have not yet been elucidated.

The CC chemokines (β - chemokines), macrophage inflammatory protein (MIP) - 1α, MIP-1β and regulated upon activation of normal T cell expressed and secreted (RANTES) are the major group of chemotactic cytokines that involving the crucial mechanisms of HIV viral entry (14,15,16). They inhibit infection of different cell lines and primary CD4 + T cells by macrophage-tropic (M-tropic) HIV isolates (14,15,17). This is because CC chemokine receptor type 5 (CCR-5) is the receptor for these chemokines and simultaneously as a major coreceptor for several M-tropic HIV strains beyond the primary CD4 receptor (16). CCR-5 tropic HIV replication in monocyte/macrophages can induce the production and expression of MIP-1α both *in vivo* and *in vitro* (18,19). From the study of endogenous chemokine levels measured by EIA, in different disease progression revealed that RANTES and MIP-1β production by PBMC from long term nonprogressors (LTNP) was not significantly different from progressive individuals. But PHA-driven production of both chemokines was significantly higher in LTNP, suggesting that *in vivo* activating stimuli might curtail HIV replication by inducing these chemokines (20). And PHA - stimulated PBMC production of the CC chemokines (MIP-1α and RANTES) were significantly higher in both asymptomatic and progressive individuals than in HIV seronegative controls. However, no significant difference in these β-chemokines from the activated peripheral blood cells was observed between healthy infected subjects and AIDS patients(21).

As monocyte/macrophage functions were dysregulated and impaired in the advanced stage of HIV infection, and these are a major source of IL-18, RANTES and MIP-1α, it could be postulated that these cytokine, chemokines may be declined in AIDS patients. The roles of IL-18, RANTES and

MIP-1α in the preferential response in Th1, which may decline in late HIV disease, are also valid for studying its dysregulation in HIV infection. This study is to investigate the qualitative expression of IL-18, RANTES and MIP-1α in PBMC of HIV-infected persons with high versus low CD4+ T cell counts in comparison to HIV seronegative healthy donors.