CHAPTER I

INTRODUCTION

Human immunodeficiency virus (HIV) is a member of the lentivirus genus, Retroviridae family. It has been clearly identified as the causative agent of the acquired immune deficiency syndrome (AIDS).[1,2,3] This disease resulted from the destruction of target cells, mainly CD4+ T lymphocytes, by several mechanisms including cytopathic effect, syncytium formation, apoptosis, and dysregulation of cytokine production.[4,5,6,7,8] HIV infection is a chronic infection the pathogenesis of which is involved in dysregulation of cytokines. Alteration of cytokine production contributing to HIV pathogenesis could be explained by two mechanisms. First, the high levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6) increase viral replication.[9,10,11] Second, the reduction of immunoregulatory cytokines such as interleukin-2 (IL-2) and interleukin-12 (IL-12) reduces cellular immunity against the virus.[12,13,14] The reductions of these cytokines and the number of CD4+ T cells lead to the high incidence of opportunistic infections and virally associated malignancies in advanced HIV-infected patients.

Chemokines or chemoattractant cytokines, a superfamily of small structural proteins (6-14 kDa), exhibit proinflammatory properties and are involved in the recruitment and activation of leukocytes to inflammatory lesions.[15,16] Chemokines consist of two major groups called α-chemokines and β-chemokines. The α-chemokines act predominantly on neutrophils and β-chemokines modulate T cell and macrophage responses. Recently, chemokines have gained great importance in HIV infection as chemokine receptors i.e., CCR5 and CXCR4 have found to be HIV co-receptors.[17,18,19,20,21] And the natural CCR5 ligands: RANTES, MIP-α and MIP-1β can inhibit cellular entry of M-tropic strain.[22,23,24,25,26] Although β-chemokines and their receptors play an very important role in the pathogenesis of HIV infection, the exact roles of β-chemokines in disease progression remain unclear. There are some studies analysed circulating levels of RANTES in HIV-infected patients, but the results are somewhat conflicting.[27,28,29,30] McKenzie et al.[27] found that the serum levels of RANTES in long-term non progressor (LTNP) individuals did not differ

from those in AIDS patients, whereas Zanussi et al.[28] showed that elevated levels of RANTES and MIP-1α are not present in LTNP individuals, but are associated with HIV disease progression. Other studies demonstrated that elevated β-chemokine mRNA expression is present in lymph nodes and brain tissue from HIV-infected patients with AIDS dementia.[31,32] Nevertheless, *in vivo* β-chemokine mRNA expression in peripheral blood mononuclear cells (PBMC) of HIV-infected individuals has not been reported.

Interleukin 18 (IL-18), originally termed IFN-γ inducing factor (IGIF), is a novel cytokine which resembles IL-1 structurally and IL-12 functionally but exerts its effect independently of both.[33,34] Although the biological functions of mouse IL-18 have been studied extensively during the last two years after the isolation of cDNA, the data obtain so far are still limited. IL-18 has been shown to have a synergistic effect with IL-12 on IFN-γ production, thus, it may play a major role in the regulation of Th1-type immune response.[35,36] In humans, elevated levels of biologically active IL-18 were observed in the synovial fluid and serum of patients with rheumatoid arthritis. This result suggests that IL-18 may be involved in chronic inflammation. Recently, IL-18 was found to stimulate HIV production in the chronically infected U1 monocytic cell line[37]

Treatment of HIV infection currently revolves around highly active antiretroviral therapy (HAART) and specifically the use of nucleoside analogues and protease inhibitors.[38] Antiretroviral therapy, however, has shown to have less impressive improvements of the immune function.[39] To that end, the use of immune modulators may be a promising approach contributing to immunological improvement and longer survival. IL-2 plays a central role in regulation of cellular immune responses by induction of T cell proliferation, enhancement of NK cell function, and stimulation of lymphokine production.[40,41,42] Kovacs and colleagues[43] have reported their results of a combination of intravenous (i.v.) IL-2 plus oral antiretroviral therapy in HIV-infected patients. Intermittent i.v. infusion of IL-2 (6-12 MIU daily for 5 days every 8 weeks) had lead to a sustained increase in the CD4 cell count to unprecedented levels in some patients, particularly in those with baseline CD4 cell counts $\geq$ 200 cells/cu.mm. Major limitations to IL-2 therapy by continuous i.v. infusion are the

relative inconvenience and the high degree of dose-limiting toxicities. Recently, Davey and colleagues[44] have studied the safety and efficacy of IL-2 therapy administered by daily subcutaneous (s.c.) injection. Their results demonstrated that the maximally tolerated dose (MTD) of IL-2 was 15 MIU/day and patients with higher baseline counts appeared to have a greater CD4 cell response. De Paoli and colleagues[45] have studied the effects of s.c.IL-2 therapy on CD4 subsets and *in vitro* cytokine production in HIV+ subjects. They found that IL-2 can induce the reconstitution of CD4/CD45RA+ (naive) lymphocyte subsets and recover the ability of these cells to produce IL-2, IL-4 and IFN-γ *in vitro*. However, the effects of IL-2 administration on *in vivo* cytokine and β-chemokine productions in HIV-infected patients are not known. This study was performed to investigate the effects of IL-2 given subcutaneously on cytokine (IL-2 and IL-18) and chemokine (RANTES and MIP-1α) mRNA productions in HIV-infected patients following different doses of s.c. IL-2 therapy in combination with antiretrovirals in comparison with antiretroviral treatment alone.