CHAPTER I

INTRODUCTION

The word "chemokine" is derived from chemoattractant, a soluble factor that attracts white blood cells to places where they are needed (e.g., sites of inflammation or infection). Lymphokine is a chemical messenger that conveys important information between lymphocytes (T-cells and B-cells). Chemokines bridge the communication gap between lymphocytes and other cells of the immune system. Chemokines are known to induce inflammation and to direct the migration of white blood cells. Chemokines are small, with molecular weight in the range of 8 to 12 kD (100 to 125 amino acid long). Four different classes have been defined, based on the location of four conserved cysteine residues; the first two residues can be adjacent (CC) separated by one (CXC) or three residues (CX3C), or can even lack one of the cysteines (C).[1,2]

Since 1995, chemokine and their receptors have been shown to act as competitive inhibitors and co-receptors in human immunodeficiency virus (HIV) infection.[3] Two of the four different classes of chemokine receptors have been shown to be of importance in HIV infection and pathogenesis, i.e., those for the CC chemokines (CCR) and those for the CXC chemokines (CXCR). [4,5]

The fist indication of the role of chemokine receptors in HIV disease came when it was shown that the chemokines RANTES (regulated upon activation, normal T expressed and secreted), MIP-1α and MIP-1β (macrophage inflammatory protein 1 alpha and beta) inhibit the growth of primary HIV isolated *in vitro*.[6] It is now clear that there are two major co-receptors for HIV required to facilitate viral binding and cell entry. The chemokine receptor CCR5 is a co-receptor for macrophage (M) tropic HIV strains, which predominate at the early, asymptomatic stage of HIV disease. The CXCR4 receptor is used as a co-receptor by T-cell line (T) tropic strains that are characteristic of later stages of infection. Many strains of HIV have been shown to use other chemokine receptors in *in vitro* studies, including CCR2, CCR3, CCR8, and CCR9. [3,4,5,7,8]

The study of the role that chemokines and chemokine receptors play in the pathogenesis of AIDS is rapidly progressing. Four naturally occurring mutations have been described in genes coding for chemokine receptors or their ligands, that influence HIV infection or disease progression namely: CCRΔ32,[9,10,11] CCR5-m303,[11] CCR2-64I [12,13,14,15] and SDF1-3'A [12,16,17]

The most studied mutation of importance in host genetic resistant to HIV infection is a 32 nucleotide (nt) deletion in CCR5 coding gene (CCR5Δ32) that results in truncation of the CCR5 protein and abrogation of its HIV co-receptor function. Individuals homozygous for this mutation are highly resistant to HIV infection.[9,10,17] Population surveys of this allele estimate a frequency of approximately 10% in Caucasian population; but it has been found to be absent or present only at very low levels in Asian and African populations.[17] CCR5-m303 is an independent mutation in the CCR5 gene; a single nucleotide polymorphism, thymidine (T) to adenine(A) substitution at position 303, that also leads to lack of CCR5 on the cell surface in homozygotes.[11]

Other discoveries have been made of additional gene variants affecting the rate of progression of AIDS. One is the gene for chemokine receptor CCR2, which is a co-receptor for only few HIV strains.[4,5,8] The CCR2-64I polymorphism cause a conservative amino acid change, valine to isoleucine, at position 64 in the first transmembrane domain of CCR2.[13,14] The allele frequency of this polymorphism varies from 10-26 %, depending on ethnic population.[13,14,19,20] In its homozygous state, this allele is associated with a 2- to 4-year delay in the progression of HIV infection to AIDS.[13]

The other mutant gene identified codes not for a receptor but for its chief ligand, stromal-derived factor-1 (SDF1). The receptor of this chemokine is CXCR4, utilized by HIV to enter a broad spectrum of T cells. SDF1-3'A, a common polymorphism that influences HIV pathogenesis, is a G to A mutation at nucleotide position 801 in the 3' untranslated region of this gene.[16] SDF1-3'A allele frequency ranges widely across

ethnic group from 3-71%.[12,16,17,21,22] Frequencies from between 24.4-36.6 %[16,21,22] have been reported in Asian populations and very high frequencies have been found in New Guinean, Melanesian and Australia Aboriginal populations (53.6-71.4 %).[22] SDF1-3'A, like CCR2-64I, is associated with delayed progression to AIDS in homozygous individuals.[12,16,17]

The reason for the uneven distribution of these alleles among human populations is unclear. Whereas CCR2-64I occurs at relatively constant frequency across racial groups, SDF1-3'A varies significantly in its distribution, indicating a possible "bottleneck" event or positive selection pressure in some racial groups in recent evolutionary history. Previous studies to estimate the frequency of these alleles in Asian population have examined small numbers of individuals or have not specified the precise racial background of the subjects. The Thai are a distinct ethnically and geographically defined population in South East Asia. Additionally, this population is experiencing an HIV epidemic, spreading largely through heterosexual contact. This study was undertaken to determine the frequencies of CCR2-64I and SDF1-3'A alleles in Thai population by the examination of 200 healthy blood donors.