CHAPTER I

INTRODUCTION

CD8$^+$ T lymphocytes are believed to play an important role in the control of viral replication during Human Immunodeficiency Virus (HIV) infection. Studies in Simian Immunodeficiency Virus (SIV)-macaque model showed that CD8$^+$ depleted SIV-infected monkeys were more progressive to AIDS than control monkeys which their CD8$^+$ T lymphocytes were not depleted (1). Moreover, adoptive transfer of CD8$^+$ T lymphocytes led to a decrease in plasma viral load to levels seen before CD8$^+$ T lymphocytes depletion. In humans, evidence supporting a protective role of CD8$^+$ T lymphocytes in HIV-1-infection is less direct. In clinical study, the appearance of HIV-1-specific CD8$^+$ T lymphocytes is closely associated with the drop in plasma viral load during acute infection (2). Reduction of Gag-specific CTL responses was observed in HIV-1-infected individuals coincided with a clinical progression (3). In addition, a significant inverse correlation was observed between Gag-specific CD8$^+$ T lymphocytes frequency and plasma viral load (4). Besides, CTL responses were demonstrated in some African sex workers who remain seronegative despite definite exposure to HIV (5).

However, antigenic specificity of CD8$^+$ T lymphocytes might have different efficiency in the control of HIV-1 infection. HIV-specific responses in Highly Exposed Persistently Seronegative (HEPS) African sex workers focused strongly on epitopes rarely or never recognised in HIV-1-infected individuals. Seroconverted HEPS individuals switched to recognise epitope which were preferentially recognised by HIV-1-infected individuals. (6, 7) Therefore, it is very interesting to analyse the HIV-specific T cell specificities in HIV-1-infected person with different level of plasma HIV-RNA.

Recently, the study on CD8$^+$ T lymphocyte responses using overlapping peptides spanning all expressed HIV-1 proteins was reported. The peptides most frequently recognised and mediated strongest CD8$^+$ T lymphocyte responses were located in Nef and Gag. (8, 9) Furthermore, Nef is a viral protein for efficient HIV-1 replication and plays an important role in viral pathogenesis. It is abundantly expressed in the early phase of HIV-1 infection. Whilst Gag is most predominantly recognised by CTL during asymptomatic HIV-1 infection and Gag-specific CTL responses gradually decreased during progression to AIDS.

In present study, we analysed the magnitude and breadth of HIV-1-specific CD8$^+$ T lymphocyte responses in HIV-1-seropositive Thais with different level of HIV RNA and in high risk HIV-1-seronegative donors and their HIV-1-seropositive partners. In the case of HIV-1-seropositive Thais, the most frequently recognised peptides and the strongest responses were located in Nef, followed by p24 Gag, p17 Gag, and p2p7p1p6 Gag, respectively. The most frequently recognised peptide and the strongest responsive peptide was Nef 9 (TYKGAFDSFFLKEKGGL). The number of epitopes targeted per subject ranged from 0 to 12 peptides (median, 3). The magnitude of responses ranged from 0 to 17,124 SFU/million PBMC (median, 836 SFU/million PBMC). However, neither the breadth nor the magnitude of HIV-1-specific CD8$^+$ T lymphocyte responses correlated with plasma viral load. In subgroup analysis, there were no significant differences of responses among subgroups (which were classified according to level of HIV-RNA). Interestingly, analysis of HIV-specific CD8$^+$ T lymphocyte responses in discordant couples demonstrated that specificities of the Nef-specific T cells were different between HEPS (Nef 7, Nef 8, Nef 9) and their infected partners (Nef 9, Nef 14, Nf 15). These results may indicate that the responses against Nef 7 and Nef 8 play a critical role in control of HIV-1 infection. In addition, we also illustrated that most subjects lacking responses against Nef protein had amino acid mutations either within epitope or in the flanking region. In this study, the frequency of Gag-specific T cells was lower than reported in other studies. This might be due to sequence variation of the enrolled donors which differed from Gag peptides used in this study.