

学位論文抄録

# Functions of HIV-1-specific CD4<sup>+</sup> T cells

(H I V - 1 特異的 C D 4 陽性 T 細胞の機能に関する研究)

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## Abstract of the Thesis

**Background and Purpose:** A restricted number of studies have shown that HIV-1-specific CD4<sup>+</sup> cytotoxic T lymphocytes (CTL) are present in HIV-1-infected individuals. In this study, I investigated the abilities of Nef-specific CD4<sup>+</sup> T cells to kill HIV-1-infected primary human cells, and to suppress HIV-1 replication in these HIV-1-infected target cells, for clarifying the roles of HIV-1-specific CD4<sup>+</sup> T cells in the control of HIV-1 infection.

**Methods:** I identified CD4<sup>+</sup> T cell epitopes by screening a Nef peptide library comprising 32 17-mer peptides for the ability of the peptide(s) to induce IFN- $\gamma$  production of CD4<sup>+</sup> T cells from HIV-1-seropositive donors. CTL activity of Nef-specific CD4<sup>+</sup> T cell clones was measured by standard chromium release assays, while cytolytic molecule expression, CD107a surface mobilization, and cytokine production of these Nef-specific CD4<sup>+</sup> T cells were measured by intracellular staining and FACS. The ability of the CD4<sup>+</sup> CTL to suppress virus replication in HIV-1-infected cells was tested by using ELISA for p24 present in the HIV-1-infected cell cultures. In addition, plasma HIV-1 from patients was sequenced to investigate the mutations on CD4<sup>+</sup> T cell epitopes.

**Results:** I identified two novel CD4<sup>+</sup> T cell epitopes, Nef37-53 and Nef187-203, which restricted by HLA-DRB1\*0403 and HLA-DRB1\*0803 respectively. Nef187-203-specific CD4<sup>+</sup> T cell clones exhibited strong cytotoxic ability towards the HIV-1-infected macrophages and CD4<sup>+</sup> T cells from an HLA-DR-compatible donor. In addition, the Nef187-203-specific cytotoxic CD4<sup>+</sup> T cell clones exhibited strong ability to suppress HIV-1 replication in both macrophages and in CD4<sup>+</sup> T cells. I detected cytotoxic potential of Nef187-203-specific CD4<sup>+</sup> T cells directly *ex vivo* in two donors, by measuring CD107a surface mobilization. Furthermore, I found that a flanking Y-to-F substitution of Nef187-203 epitope is associated with the epitope's restriction allele HLA-DRB1\*0803 in Japanese HIV-1-chronically infected population.

**Discussion:** Nef-specific CD4<sup>+</sup> CTLs may target HIV-1-infected host cells that resist CD8<sup>+</sup> CTL recognition due to the impaired HLA class I antigen-processing pathway. Thus, particularly in the tissues that can express HLA class II molecules, i.e., dendritic cells, macrophages, and activated CD4<sup>+</sup> T cells, CD4<sup>+</sup> CTLs may take the position left vacant due to escape from CD8<sup>+</sup> CTL surveillance.

**Conclusions:** My results suggested that HIV-1-specific CD4<sup>+</sup> T cells could directly control HIV-1-infection *in vivo* by killing HIV-1-infected cells and suppressing virus replication in the HIV-1-infected host cells.