学位論文抄録

Impact of HLA class I-associated genetic variability in HIV-1 accessory gene *vpu*

（HLA クラス I が HIV-1 アクセサリー遺伝子 *vpu* の多型性に及ぼす影響）

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Abstract of the Thesis

[Background and purpose] HLA class I (HLA-I) restricted CTL responses drive HIV evolution through selection of sequence polymorphisms and represent a major selective force toward HIV-1 proteins such as Gag and Nef. Now-a-days it is well known that an accessory protein Vpu acts as crucial enhancer in HIV-1 pathogenesis. Although Vpu represents one of the most variable proteins in the HIV-1 proteome, it is still elusive to what extent HLA-I influence its evolution.

[Methods] The *vpu* genes were amplified by nested-PCR using plasma viruses isolated from HLA-I-typed, treatment-naive, chronically-infected individuals in Japan (n=240). The statistical analysis was performed with a phylogenetically-informed method incorporating the effects of HIV codon co-variation and linkage disequilibrium among HLA-I alleles. Multiple tests were addressed using false discovery rate (q<0.2).

[Results & Discussion] We successfully obtained vpu sequence from 216 out of 240 samples tested. Most codons of Vpu displayed substantial variability, with the average entropy score reaching 0.58. The pattern of amino acid variability was consistent with those observed in HIV-1 subtype B. We only identified 4 different significant HLA-HIV amino acid associations from 3 codons of Vpu, from primary and alternative reading frames (ARFs) of Vpu, suggesting that HLA-I had minor effects on Vpu variability. A mutation arginine (R) to lysine (K) being significantly enriched in subjects having HLA-A*33:03 at position 37 of Vpu, one of the highly immune-dominant epitopic region. Remarkably, we have identified a non-synonymous mutation in Env while the corresponding position is synonymous in Vpu in patients having HLA-B*40:01. However, despite its small size (81 amino acids), Vpu showed 103 codon-codon associations, suggesting that conformation and function may be preserved through many possible combinations of primary and secondary polymorphisms. Noticeably, we also identified a statistically significant association between amino acid residues at position 5 with plasma viral load and therefore it would be interesting to examine further functional effects of amino acid polymorphisms at position 5.

[Conclusion] Taken together, we conclude that the influence of HLA-I alleles on Vpu evolution at the population level showed lesser extent compared to other highly variable HIV-1 accessory proteins, providing us with additional insight into differential evolutional pathways among viral accessory proteins.