



**Karolinska
Institutet**

Institutionen för Laboratoriemedicin

Unifying Viral Evolution and Immunological Patterns to Investigate Risk of HIV-1 Disease Progression

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i sal 4Z, Alfred Nobels Allé 8, Huddinge

Tisdagen den 18 december, 2012, kl 09.00

av

Melissa M Norström

Civilingenjör

Huvudhandledare:

Docent Annika C Karlsson
Karolinska Institutet
Institutionen för
Laboratoriemedicin

Bihandledare:

Docent Adnane Achour
Karolinska Institutet
Centrum för
Infektionsmedicin

Dr. Jakob Michaëlsson
Karolinska Institutet
Centrum för
Infektionsmedicin

Prof. Klas Kärre
Karolinska Institutet
Institutionen för Mikrobiologi,
Tumör och Cellbiologi

Fakultetsopponent:

Prof. Sarah Rowland Jones
University of Oxford
Weatherall Institute of
Molecular Medicine

Betygsnämnd:

Prof. Patrik Medstrand
Lunds Universitet
Institutionen för
Laboratoriemedicin

Prof. Anna Karlsson
Karolinska Institutet
Institutionen för
Laboratoriemedicin

Docent Sören Andersson
Örebro Universitetssjukhus
Institutionen för
Laboratoriemedicin

Stockholm 2012

ABSTRACT

After 30 years of research, the exact mechanisms underlying human immunodeficiency virus type 1 (HIV-1) pathogenesis and disease progression remain elusive. In the absence of highly active antiretroviral therapy, most HIV-infected individuals progress to AIDS within 10 years. The clinical course of HIV-1 infection is characterized by considerable variability in the rate of disease progression among patients with different genetic background. It has been shown that the rate of progression can depend on the expression of certain human leukocyte antigen (HLA) class I alleles that present antigen to the host immune system. The HLA-B*5701 allele is most strongly associated with slower progression. Underlying mechanisms are not fully understood but likely involve both immunological and virological dynamics. In this thesis, viral evolution and immunological patterns were studied in the context of HIV-1 risk of disease progression in HLA-B*5701 subjects and non-HLA-B*57 control subjects.

First, HIV-1 *in vivo* evolution and epitope-specific CD8⁺ T cell responses were investigated in six untreated HLA-B*5701 patients monitored from early infection up to seven years post-infection. The subjects were classified as high-risk progressors (HRPs) or low-risk progressors (LRPs) based on viral load and baseline CD4⁺ T cell counts. Interestingly, polyfunctional CD8⁺ T cell responses were more robust in LRPs, who also showed significantly higher interleukin-2 production in early infection compared to HRPs. Additionally, HIV-1 *gag* p24 sequences exhibited more constrained mutational patterns with significantly lower diversity and intra-host evolutionary rates in LRPs than HRPs. Further in-depth analyses revealed that the difference in evolutionary rates was mainly due to significantly lower HIV-1 synonymous substitution [replication] rates in LRPs than HRPs. The viral quasispecies infecting LRPs was also characterized by a slower increase in synonymous divergence over time. This pattern did not correlate to differences in viral fitness, as measured by *in vitro* replication capacity, but a significant inverse correlation between baseline CD4⁺ T cell counts and mean HIV-1 synonymous rate was found. The results indicate that HLA-linked immune responses in HLA-B*5701 subjects who maintain high CD4⁺ T cell counts in early infection are more likely to control HIV-1 replication for an extended time.

To further assess these findings and evaluate them in the context of viral population dynamics, a new method was implemented to investigate the temporal structure of phylogenetic trees inferred from HIV-1 intra-host longitudinal samples. The analysis revealed that changes in viral effective population size (N_e) over time were more constrained in HLA-B*5701 subjects compared to non-HLA-B*57 controls, possibly due to the different evolutionary dynamics of archival viral strains observed in the two groups of patients.

Explaining the differences in risk of HIV-1 disease progression among HLA-B*5701 subjects, as well as between HLA-B*5701 and non-HLA-B*57 subjects, could have significant translational impact by providing specific correlates of protection that are essential for the successful development of a vaccine. Ultimately, the present work demonstrates that a thorough understanding of HIV-1 pathogenesis and disease progression requires a multidisciplinary approach unifying viral evolution and immunological patterns.