Cellular immunity driving HIV-1 evolution

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Summary
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Transmission of HIV-1 results in an acute infection, followed by an asymptomatic period of on average about 8 years. In the absence of antiretroviral therapy, most patients progress into a generalized immune dysfunction that culminates in death. The length of the asymptomatic period varies, and in rare cases individuals do not progress to AIDS despite a seropositive follow-up of more than 25 years. These unique cases highlight the fact that susceptibility to HIV-1 infection and progression to disease are complex traits modulated by environmental and genetic host factors. Evidence has indicated that natural variations in host genes can influence the outcome of HIV-1 infection and its transmission. In this thesis we studied HIV-1 evolution in relation to several host factors. Chapter 2 validates the virus isolation procedure used for several studies described in this thesis. Chapters 3-9 describe the influence of immune pressure, in particular the host CTL response, on viral evolution. Chapter 10 is a case-report illustrating the importance of host factors in determining the outcome of infection. Chapters 11-12 describe the effect of 2 non-immune host factors (CCR5 and TRIM5α) on viral evolution. Chapter 13 describes the current knowledge on HIV-specific cellular immunity.

HIV-1-infected individuals at all times during infection harbor a swarm of related but slightly different virus variants that coexist in the so called viral quasispecies. In general, patient plasma is used to study viral evolution. However, to study viral evolution in the context of the biological properties of replication competent HIV-1 in vitro, virus isolation is required. To obtain a swarm of co-existing virus variants representative for the quasispecies in vivo, HIV-1-infected patient PBMCs can be cocultured under limiting dilution conditions with target cells in multiple parallel cocultures. To determine whether these clonal HIV-1 variants are indeed representative of the in vivo quasispecies, they were compared to the HIV-1 quasispecies present in plasma from the same subjects at the same time points (Chapter 2). Comparing the sequences for gag, env and nef, we found that in most cases the clonal HIV-1 variants accurately represented the viral quasispecies in plasma within a single individual.

Characterization of primary HIV-1 infection will increase the understanding of HIV-1 pathogenesis. In Chapter 3 we analyzed sequence evolution in the viral genes gag, nef and gp120 env during and following primary HIV-1 infection in 8 therapy-naive individuals. During the first weeks after SC, HIV-1 diversity and divergence was extremely low. In addition, both the numbers of synonymous (dS) and non-synonymous (dN) mutations were very low and selection pressure, measured as dN/dS ratio, was low. Between 1.8 and 10.5 ± 3.3 months post SC, HIV-1 evolution in gag was dominated by reverting mutations, in gp120 env forward and reverting mutations contributed equally to the amino acid sequence changes while in nef forward mutations dominated. At later time points (>10.5 ± 3.3 months post SC) diversity was higher and HIV-1 evolution in the three genes was dominated by forward mutations. Throughout the course of infection forward mutations occurred mainly (60-70%) within epitopes restricted by the HLA of the patient.

To analyze the dynamics of potential CTL escape mutations in donor-HLA-restricted epitopes after transmission, we studied sequence changes in HIV-1 variants isolated from known HLA disparate donor-recipient pairs. Directly after transmission the majority of donor-derived mutations in and outside donor-HLA-restricted epitopes in gag, nef, and env
were preserved in the recipient. One to two years after transmission low numbers of both reverting and forward mutations had occurred. During subsequent long-term follow-up, sequence dynamics was dominated by forward mutations, mostly (50–85%) in recipient-HLA-restricted CTL epitopes. At the end of long-term follow-up, on average 43% of the transmitted CTL escape mutations in donor-HLA-restricted epitopes had reverted to the subtype B consensus sequence (Chapter 4).

In the Amsterdam Cohort of HIV-infected homosexual men, HLA B57 is overrepresented among HIV-1-infected long-term nonprogressors (LTNPs), although progression to AIDS is found in 50% of HLA B57 individuals. It has been suggested that the association between HLA B57/5801 and asymptomatic survival is a consequence of strong CTL responses against epitopes in the viral proteins, especially in gag. Moreover, CTL escape mutations in gag would coincide with viral attenuation, resulting in low viral load despite evasion from immune control. In our study we found similar frequencies of HIV-1 gag specific CTL responses and similar numbers of escape mutations in HLA B57 epitopes between LTNPs and progressors with HLA B57, however the HIV-1 variants from HLA B57 LTNPs had a much lower replicative capacity as compared to viruses from HLA B57 progressors (Chapter 5). Additionally, we observed that nonprogression in HIV-infected HLA B57 individuals was associated with preserved CD8+ T lymphocyte responsiveness to the HW9 epitope in nef (Chapter 6).

Recently, it was found that a single nucleotide polymorphism (SNP) in the HCP5 gene is known to be in high linkage disequilibrium (LD) with the protective HLA B*5701 allele. Therefore it was hypothesized that the association between this polymorphism in HCP5 and a low viral load set point could in fact be due to the protective effect of HLA B*5701. In Chapter 7, we provide evidence that the effect of this SNP in the HCP5 gene on the clinical course is in indeed the effect mediated by HLA B*5701.

By comparing the within-host evolution of CTL responses directed towards HIV-1 epitopes presented via protective and non-protective HLA alleles, we tested the hypothesis that HLA alleles associated with slow disease progression are protective because they specifically present the most conserved parts of the HIV proteome. CTL responses restricted by HLA A2 are generally less well-preserved during disease progression than CTL responses restricted by protective HLA alleles, in individuals expressing either one of these alleles. In contrast, when comparing the preservation of CTL restricted by HLA A2 or one of the protective HLA molecules in individuals co-expressing these HLA alleles, CTL responses restricted by the protective HLA alleles were found to be lost at least as fast as CTL responses restricted by HLA A2. The observed loss of CTL responses was due to a combination of CTL escape mutations and functional impairment of HIV-1 specific T cells. Thus, the association between the protective HLA B27 and B57 alleles and relatively slow HIV-1 disease progression is not due to specific presentation of the most conserved parts of the HIV-1 proteome (Chapter 8).

Escape from CTL responses does not only affect within host evolution but is also thought to affect the ongoing evolution of the HIV-1 at a population level. In Chapter 9 we studied adaptations to HLA alleles at the population level by comparison of viral sequences derived
from individuals who seroconverted recently (2005/2006) with those who seroconverted early (1985) during the HIV-1 epidemic in Amsterdam. HIV-1 strains isolated from recent seroconvertors were found to contain a significantly lower number of 9-mers predicted to bind to the 5 HLA B alleles under investigation compared to historical HIV-1 strains. In contrast, no difference was observed for the number of 9-mers restricted by the 5 HLA A alleles studied. Remarkably, the reduction in the number of CTL epitopes during the epidemic observed for HLA B alleles was not due to adaptation to the most common HLA B alleles, but instead to 2 alleles associated with slow progression to AIDS, HLA B27 and B57.

Chapter 10 describes a case report on a HIV-1 superinfection event in a natural elite controller who subsequently established relative control over the superinfecting virus while the same virus variant was associated with a 1.5 log higher viral load and a progressive disease course in his two partners. Thus, in this superinfected individual host mechanisms seem to be able to repeatedly control HIV-1 replication thus halting disease progression. Both immune pressure (CTL) and other host factors may be responsible for this ability.

Upon the identification of the C-C chemokine receptor 5 (CCR5) as a major coreceptor for HIV-1 infection, certain individuals who had remained uninfected despite multiple exposures to HIV-1, were found to be homozygous for a 32 base pair deletion in the CCR5 gene (CCR5 Δ32). HIV-1-infected individuals heterozygous for CCR5 Δ32 in general express lower levels of CCR5 and progress more slowly to AIDS than individuals who are homozygous for the wild-type CCR5 allele. In Chapter 11 we describe that viral envelopes from CCR5 Δ32 heterozygous individuals showed slower evolutionary rate and a tendency for stronger positive selection pressure on the variable regions of gp120 env as compared to CCR5 WT/WT individuals. Furthermore, CCR5Δ32 heterozygous individuals had lower percentages of CCR5+ CD4+ memory T cells and lower CCR5 expression, and their viruses had lower susceptibility to inhibition by the CCR5 ligand RANTES early in infection. Overall, this suggests that there is a strong influence of CCR5 host genetic background on the evolution of R5 HIV-1 variants, and that optimization of the virus co-receptor use is driven by target cell availability and co-receptor expression levels.

Chapter 12 describes the analyses of HIV-1 variants from participants of the Amsterdam Cohort Studies for the presence of Trim5α escape mutations in capsid and the effect of these escape mutations on the clinical course of infection. Recently, Trim5α has been identified as an inhibitory factor blocking infection of a broad range of retroviruses in a species specific manner. Human Trim5α inhibits HIV-1 replication in vitro, implying that Trim5α may contribute to host control of HIV-1 replication in vivo. Trim5α escape mutants emerged in the late phase of infection and were ultimately present in 13.7% of HIV-1 infected individuals. These patients had a significantly lower set-point plasma viral RNA load and a prolonged asymptomatic survival as compared to individuals who lacked Trim5α escape mutants. This protective effect was stronger in individuals who later developed X4 variants. In addition, X4 emergence was delayed in individuals who later developed Trim5α escape variants, compatible with suppression of viral replication.
The implications of current knowledge on HIV-specific cellular immunity for vaccine development are discussed in Chapter 13.