Cellular immunity driving HIV-1 evolution
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Chapter 1

General introduction and outline of this thesis
General introduction

In 1981 the first reports appeared on a new disease among young homosexual/bisexual men in New York and Los Angeles. These men were suffering and dying from immune deficiency characterized by opportunistic infections or malignancies. At that time it could not be predicted that the virus that caused this immune deficiency would become one of the leading causes of death in the world to date. Since its identification as the pathogenic cause of the Acquired Immunodeficiency Syndrome (AIDS), human immunodeficiency virus type 1 (HIV-1) has emerged as a major global pandemic with an estimated 33 million infected individuals worldwide at the end of 2007 (UNAIDS/WHO, AIDS epidemic update 2007 www.unaids.org). Although improvements in antiretroviral therapy have dramatically reduced HIV-1 related morbidity and mortality among those with access to treatment, the search for an effective HIV-1 vaccine continues.

The variable course of HIV-1 infection

The clinical course of HIV-1 infection can be highly variable and is characterized by a gradual and progressive loss of CD4+ T cells and cellular immunity, eventually resulting in the development of AIDS. During primary infection high viral load levels can be observed. The level of viremia reaches a peak which is mirrored by a quick loss of CD4 cells in the peripheral blood. Hereafter a decline of viremia can be seen that subsequently settles at a generally lower steady level, the viral load set point. This decline may be a consequence of an effective immune response or a reduction of virus production as a consequence of a limitation in the number of target cells. One to two years after seroconversion this viral load set point is established and can be maintained for variable number of years during asymptomatic infection. The viral RNA set point has been shown to be predictive for the subsequent clinical course of HIV-1 infection.

Although there may be a clinically latent or asymptomatic phase in the course of HIV-1 infection, at most times virus replication and turnover are high, which in combination with the error-prone nature of HIV-1 reverse transcriptase and its lack of proofreading results in a continuous emergence of new HIV-1 variants. The generation of new HIV-1 mutated variants facilitates escape from host immune pressure, and selection for optimal biological properties such as coreceptor use and replication capacity. Due to selection, the genetic diversity of virus populations at a given time point is relatively low. 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 the absence of antiviral therapy the majority of the infected individuals (70-80%) experience typical disease progression in which they develop AIDS within 7-11 years after infection. Ten to 15% of the individuals are rapid progressors who have a fast CD4+ T cell decline and develop AIDS within a few years after infection (Figure 1). The long-term nonprogressors (LTPNPs) (5%) can remain healthy in the absence of antiviral therapy for over 10 years while elite controllers (<1%) have viral RNA load in plasma of <50 copies ml on at least three occasions during a 1 year period. Differences in both host as well as viral factors have been associated with differences in HIV-1 disease progression.
Viral factors and the course of HIV-1 infection

The variability in the clinical course of HIV-1 infection is due to viral as well as host factors. One of the viral properties that most prominently correlates with disease progression is the ability to switch coreceptor usage. Entry into target cells is a multi-step process. In addition to CD4, HIV-1 requires a chemokine receptor as a coreceptor to enter the cell. Chemokine receptors CCR5 and CXCR4 are the most important coreceptors in vivo. Cell tropism of HIV-1 isolates is determined by specificity of the envelope glycoprotein for the coreceptor, either CCR5 or CXCR4. CCR5-using HIV-1 variants (R5 variants) can infect macrophages and memory T cells whereas CXCR4-using viruses (X4 variants) can infect memory as well as naive T cells. In general, R5 variants are responsible for the primary infection, both after horizontal as well as vertical transmission, and persist throughout the course of infection. In approximately 50% of the infected individuals X4 variants evolve from R5 variants and can either co-exist with R5 variants or replace them in the quasispecies. The emergence of X4 variants is associated with accelerated decline in CD4+ T cells and a faster progression to disease. Furthermore, several studies and case reports have shown that mutations or deletions in the virus, for instance in the nef gene, can lead to attenuated virus and/or prolonged asymptomatic survival.

Genetic host factors and the course of infection

In addition to viral factors, genetic host factors are considered to partly explain the differences in clinical course of disease in infected individuals. One of the most consistent host factors associated with differences in disease progression is the presence of certain HLA alleles, particularly HLA B alleles. HLA B57, HLA B5801 and HLA B27 are strongly enriched in LTNPs whereas HLA B35 and Cw4 are associated with a faster disease progression. HLA molecules present peptides to cytotoxic T lymphocytes (CTLs) and provide the mechanism by which the immune system generates a specific response to a pathogen. A temporal relationship exists between the appearance of HIV-1 specific CTLs in vivo and the decline of acute-phase viremia. This correlation together
with the epidemiological link between specific HLA class I alleles and different rates of
disease progression suggest that the quality of the CTL response and/or the characteristics of targeted epitopes strongly influences the effectiveness of antiviral control by cellular immunity. However, the strongest evidence supporting CTLs as a major determinant of HIV-1 control may be mutational immune escape. First described in 1997, selection of viral escape mutations during primary and chronic HIV-1 infection identified immune-driven evolution as a continuous process occurring throughout the disease course.

Upon the identification of the CCR5 receptor as a major coreceptor for HIV-1 infection, individuals were identified who despite multiple exposures to HIV-1 had remained uninfected. Some of these individuals were homozygous for a deletion of 32 base pairs in the CCR5 gene. The few individuals who did get infected despite this genotype, were most likely infected by CXCR4-utilizing virus variants. HIV-1 infected individuals who were heterozygous for CCR5Δ32 in general expressed lower levels of CCR5 and progressed more slowly to AIDS than individuals who were homozygous for the wild-type CCR5 allele.

In recent years, a number of intrinsic intracellular host factors that interfere with HIV replication have been identified, but it remains to be established whether these factors play a role in the variable clinical course of HIV-1 infection. One of these host factors is APOBEC3G, a cellular enzyme that potently restricts HIV replication. This cytidine deaminase functions primarily by causing dG/dA hypermutation of the newly synthesized HIV DNA during reverse transcription. HIV circumvents this host defense system via the action of its accessory protein Vif, which targets APOBEC3G for accelerated degradation. Another mediator of innate cellular antiviral resistance is Trim5α. Trim5α is shown to modulate infection in a monkey model of AIDS through a block before the initial step in reverse transcription. Whether these host restriction factors or other yet-to-be-defined host restriction factors may modulate HIV control in humans has to be determined.

Scope of the thesis

The aim of this thesis was to study HIV-1 evolution in relation to host factors. HIV-1-infected individuals harbor at each moment in their course of infection a large number of highly related yet different virus variants that coexist in the so called viral quasispecies. Here we studied whether clonal HIV-1 variants obtained via limiting dilution assay are representative for the replication competent HIV-1 quasispecies in plasma (Chapter 2).

In Chapter 3, HIV-1 evolution during primary infection was studied. HIV-1 evolution in 5 horizontal HLA-disparate donor-recipient pairs from the Amsterdam Cohort Studies, the sequence dynamics in and outside predicted epitopes of CTLs were studied after transmission (Chapter 4).

HLA B57 and HLA B5801 have both been associated with long-term nonprogressive HIV-1 infection but the underlying protective mechanism remains to be established. In Chapters 5 and 6, we compared HIV-1 from progressors and LTNP who were all carriers of HLA B57 or HLA B5801, for sequence variation in Gag (Chapter 5) and Nef (Chapter 6) and the ability of the progressors and LTNP to generate CTL responses against HLA B57/B5801 restricted epitopes in these viral genes.
A SNP in the HCP5 gene is known to be in high linkage disequilibrium (LD) with the protective HLA B5701 allele. In Chapter 7, we provide evidence that the effect of this SNP in the HCP5 gene on the clinical course is in fact the effect mediated by HLA B*5701. In Chapter 8, the maintenance of HIV-specific CTL responses restricted by protective HLA alleles B57 and B27 and non-protective HLA allele A2 during HIV-1 disease progression were studied.

In Chapter 9, HIV-1 evolution in relation to HLA was studied. HIV-1 variants isolated early in infection from individuals who were infected in 1985 were compared with virus variants that were obtained from individuals who were infected in 2005/2006 for the prevalence of CTL epitopes or signature sequences for peptide processing.

Chapter 10 is a case report on a HIV-1-infected elite controller, who experienced a viremic episode after superinfection but regained natural viremic control while viral load in his two partners infected with the same viral strain was continuously about 30-fold higher. The effect of CCR5 Δ32 on the evolution of HIV-1 was studied in Chapter 11. 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.

The implications of current knowledge on HIV-specific cellular immunity for vaccine development are discussed in Chapter 13.

Reference List