Virus and host determinants of HIV-1 infection and AIDS pathogenesis

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Both the odds of getting HIV-1 infected upon exposure and the course of HIV-1 infection are highly variable among individuals. The studies described in this thesis focused on a number of virus and host features that influence HIV-1 infection and AIDS pathogenesis.

A general introduction on HIV-1 and AIDS pathogenesis is followed by 4 chapters (2-5) that deal with aspects of the interaction between the host and the most prevalent HIV-1 variants, namely those with an NSI phenotype. The next chapter (6) describes the dynamics of viral load during the course of infection. Changes in viral load partly reflect changes in viral fitness and in that respect this chapter may be considered introductory to the 4 final chapters (7-10), which describe the evolution of viral features that enhance fitness/virulence and their influence on disease progression. The thesis is concluded with a general discussion.

In chapter 1 the current knowledge on characteristics of HIV-1 and AIDS pathogenesis are summarized. Described are the basis of virus variability and commonly occurring HIV-1 phenotypes that are associated with different stages of infection. Next, features that are known to influence transmission and the hallmarks of the acute and chronic phases of infection are summarized.

In chapter 2 factors determining HIV-1 transmission among male monogamous homosexual couples were studied. Both the cellular virus load in the potential virus donors around the moment of exposure and the susceptibility of PBMC from the exposed individuals for NSI variants of their partners were associated with HIV-1 transmission. Low susceptibility to NSI HIV-1 infection was partly associated with the presence of a 32-bp deletion in the gene encoding for the coreceptor of NSI variants, CCR5. This study confirmed the existence of differences in host susceptibility to HIV-1 infection and demonstrated the protective effect of low susceptibility on HIV-1 infection.

In chapter 3 the influence of CCR5 cell surface expression levels and production of the natural ligands of CCR5, the β-chemokines, on in vitro NSI HIV-1 susceptibility was studied. Large variation was observed in the levels of CCR5 surface expression after in vitro stimulation of PBMC, which appeared to be dissociable from the presence of the 32-bp deletion. Low CCR5 surface expression and high production of β-chemokines were associated with reduced levels of in vitro HIV-1 replication. These findings suggest that in vivo differences in CCR5 expression and β-chemokine production might influence the extent of virus production and hence the course of infection.

In chapter 4 we studied whether differences in disease progression among individuals with solely NSI variants could be attributed to evolution of the capacity to use alternative coreceptors. The coreceptor usage of NSI variants isolated early and late in infection, from individuals either or not carrying the CCR5 Δ32 mutation and from individuals with rapid or slow disease progression, were all restricted to the use of CCR5. This study showed that disease progression can occur in the sole presence of HIV-1 variants that only use CCR5 and that other factors must exist that explain the differences in disease progression among individuals with solely NSI variants.

In chapter 5 the role of CCR5 cell-surface expression levels on disease progression was studied. We showed that the proportion of cells that express CCR5 at their surfaces increases slightly during the course of infection. At comparable stages of infection however, the proportion of CCR5-expressing cells was higher in individuals who subsequently progressed to AIDS, compared to individuals who did not develop AIDS in a similar period of time. Furthermore, pre-seroconversion the proportion of CCR5-expressing cells was higher in individuals who subsequently got infected and developed AIDS at a relatively fast rate. These findings show that the degree of NSI HIV-1 coreceptor availability influences AIDS pathogenesis.

In chapter 6 one of the main parameters of disease progression, the viral load is described. We compared two commonly used measures of
viral load, the number of RNA copies in serum and the frequency of infected cells that can be induced to produce virus in vitro. The two measures correlated very well and longitudinal analysis revealed a gradual increase in either one or both measures during disease progression. The increase in circulating free virus and number of infected cells might reflect the evolution of HIV-1 variants with increased fitness.

In chapter 7 we studied whether differences in replication capacity among NSI variants could account for differences in the course of infection between individuals with NSI variants only. Late in infection the fast majority of progressors and about half of a group of long-term nonprogressors had a high virus load and harbored viruses with high replication capacity. In contrast, 4 out of 7 long-term nonprogressors persistently had variants with low replication capacity. In all individuals the viral load was associated with the in vitro replication kinetics of HIV-1 variants. The absence of evolution towards high replication kinetics might contribute to a beneficial clinical course in some individuals.

In chapter 8 the sequential events in the evolution of replication and SI capacity were studied. The evolution of SI variants could occur prior to evolution of variants with high replication kinetics. This observation, together with the existence of rapid-replicating NSI variants in the absence of SI evolution described in the previous chapter, shows that evolution of these viral characteristics is independent. After the emergence of SI variants, NSI variants remain present, and continue to expand, even when they continue to have lower replication kinetics compared to the co-existing SI variants. These data suggest a lack of competition between the two types of variants, which might be due to occupancy of different niches resulting from a different target cell range.

In chapter 9 the tropism of NSI and SI variants for different CD4+ T cell subsets is described.

CD4+ T cells of the memory subset express both CCR5 and/or CXCR4, while CD4+ T cells of the naive subset almost exclusively express CXCR4. In agreement with their coreceptor usage, NSI variants were almost exclusively detected in the memory cells, and SI variants were detected both in memory and naive cells. The frequency of naive cells infected with SI variants was associated with the rate of CD4+ T cell decline. Infection of naive T cells might interfere with the host's capacity to renew the CD4+ T cell population.

In chapter 10 the evolution of coreceptor usage and CD4+ T cell tropism was studied during NSI to SI conversion. While initially all variants solely use CCR5, the transition of the NSI to SI phenotype is accompanied by an expansion of coreceptor usage with that of CXCR4 and in some cases CCR3. At the moment of SI conversion variants could be detected that were characterized by an intermediate capacity to use CXCR4 as shown from discrepancies in their capacity to infect the MT2 cell line and the U87-CXCR4 cell line. These virus variants with intermediate phenotypes had an NSI V3 genotype. The appearance of SI variants that could efficiently use both CCR5, CXCR4 and in some cases CCR3 was followed by the emergence of SI variants that lost the capacity to use CCR5. The different stages in coreceptor evolution were temporally associated with a relative increase in the frequency of SI infected naive cells. The existence of distinct CCR5- and CXCR4-expressing CD4+ T cell populations, even within the memory compartment, provides an explanation for the co-existence of NSI and SI variants and their independent evolutionary pathways.

In chapter 11 the studies described in this thesis are incorporated in an overview of host and virus features that influence HIV-1 infection/transmission and the course of infection. Finally the interactions between virus and host and their implications on the course of infection are discussed.