T cell turnover and thymic function in HIV-1 infection
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Summary
HIV-1 infection is characterized by a gradual decline in CD4+ T cells. Initially, this has been related to high turnover-induced exhaustion of T cell production. Later, when it became clear that T cell turnover in HIV-1 infection is only modestly increased and does not lead to replicative exhaustion of T cells, CD4+ T cell loss was attributed to interference of HIV-1 with T cell renewal. Both hypotheses are addressed in this thesis.

In the first part of this thesis, the role of elevated T cell turnover in HIV-1 pathogenesis is studied. In chapter 2, the original high turnover / exhaustion model is described, followed by a brief overview of ensuing studies that led to rejection of this hypothesis. Still, the modestly elevated T cell division rates that are characteristic for HIV-1 infection were assumed to be a homeostatic response to HIV-1 induced T cell depletion at the time experimental work on this thesis was started in June 1998. In chapter 3, we used ex vivo Ki67 staining to measure peripheral T cell division rates and confirmed previous studies showing that HIV-1 infection leads to a several fold increase in CD4+ and CD8+ T cell turnover. Interestingly, this increased T cell division rapidly disappeared during HAART, long before T cell numbers were restored. This indicated that it is chronic immune activation driven by persistently replicating HIV-1, rather than a homeostatic response to T cell depletion, that pushes peripheral T cell division during HIV-1 infection. Chapter 4 describes a detailed study of the role of immune activation in a group of HIV-1 infected individuals that experienced a prolonged period of virologic failure to antiretroviral treatment. Preservation of peripheral blood CD4+ T cell numbers in some of these patients may be related to the level of immune activation that determines the distribution of lymphocytes over blood and lymphoid tissues. In addition to having such a temporal effect on peripheral blood CD4+ T cell numbers, long-term hyperactivation of the immune system actually may be a key factor in HIV-1 pathogenesis, as described in chapter 5. By investigating participants from the Amsterdam Cohort Studies on HIV-1 infection and AIDS, we found in a prospective study via multivariate survival analyses that patients with increasing peripheral CD4+ and CD8+ T cell division rates and increasing levels of immune activation have a significantly elevated risk to progress to low CD4+ T cell numbers and AIDS. In addition, pre-seroconversion low CD4+ T cell counts and increased levels of CD4+ T cell activation were associated with an increased risk to develop AIDS after HIV-1 seroconversion. These data suggest that continuous high-level virus replication may, through persistent immune hyperactivation, lead to continuous recruitment of quiescent T cells thereby eroding the CD4+ and CD8+ naive T cell pool.

In the second part of this thesis, we investigated the role of the thymus in HIV-1 pathogenesis. In chapter 6, an overview of literature available until March 1999 describing the effect of HIV-1 on thymic function in mouse models and humans is given. Until that time, it was not possible to directly assess thymic function in healthy or HIV-1 infected individuals, but at the end of 1998 a new technique
became available that was thought to allow quantification of thymic output. This technique is based on the identification of recent thymic emigrants by the presence of T cell receptor excision circles (TRECs) that are formed during T cell receptor gene rearrangements in the thymus. However, since TRECs are episomal circles, they are not replicated and are thus diluted through cell division. With mathematic modeling we showed in chapter 7 that in the healthy situation, complete abrogation of thymic output will have only little effect on TREC content, since naive T cells are generally long-lived and have low division rates. In the presence of naive T cell division, TRECs will be diluted and we found that the decrease of TREC content in HIV-1 infection is best explained by increased cell division within the naive T cell compartment. Our results show that TREC decline in HIV-1 infection is related to persistent immune activation and should not be taken as a sign of HIV-1 related thymic impairment. In chapter 8 more details on the formation of TRECs in the thymus and on the interpretation of TRECs in different clinical settings are provided. In chapter 9 we have measured TREC and peripheral T cell dynamics in a group of HIV-1 infected children before and during anti-retroviral treatment. T cell division correlated inversely with age in healthy children. HIV-1 infected children were found to have even higher peripheral T cell division rates, that declined rapidly after initiation of antiretroviral therapy. Similar to adults, TREC decline in HIV-1 infected children did not reflect suppressed thymic function. Finally, in chapter 10, we analyzed TREC and T cell decline in a group of adult patients who were initially infected with non-syncytium inducing (NSI), CCR5 using (R5) HIV-1 variants but in whom syncytium inducing (SI), CXCR4 using (X4) HIV-1 variants emerged. Using a mathematical model and the combined analysis of TREC content, TREC number and peripheral T cell division, we suggested that SI/X4-related accelerated naive CD4+ T cell decline is mainly caused by increased death of peripheral blood naive CD4+ T cells, rather than by thymic dysfunction induced by SI/X4 viruses.

These and other studies demonstrated that the role of the thymus in HIV-1 pathogenesis remains to be determined. Even more important than HIV-1 induced thymic dysfunction may be the general inability of the thymus to actively compensate for an increased loss of T cells. Indeed, recovery of naive T cell numbers in HIV-1 infected children on HAART (chapter 9) that were over 2 years of age was not faster than in adults, when related to age-matched control values. In addition, when studying a group of adult peripheral stem cell recipients, we did not find evidence for homeostatic increments of thymic output (chapter 11). TREC content recovered rapidly in these patients, but this occurred long before significant increases in naive T cell numbers could be observed. Post transplant recovery of TREC content should thus not be taken to reflect 'thymic rebound', but may best be explained by a continuous, normal production of TREC+ naive T cells that are released into a virtually empty T cell pool. Furthermore, we found that increased post transplant peripheral T cell division rates and corresponding low TREC contents were mostly related to clinical events, such as infectious
complications and graft versus host disease. Thus, also in this setting elevated peripheral T cell division rates are a sign of antigen-driven immune activation rather than homeostatic expansion of the T cell pool.

Taken together, the immune system may lack the ability to compensate for loss of naive T cells, and in chapter 12 we have postulated that it may not be exhaustion of homeostatic responses, but rather innate thymic homeostatic inability together with gradual wasting of T cell stock that leads to T lymphocyte depletion in HIV-1 infection. In chapter 13, this model is related to more recent (years 2000–2002) findings by our and other laboratories. These data suggest that it is indeed persistent hyperactivation of the immune system that leads to continuous recruitment of quiescent, naive T cells to the rapidly proliferating part of the T cell compartment. Because naive T cells are difficult to replace, this will ultimately erode the CD4⁺ and CD8⁺ naive T cell pool.