T cell turnover and thymic function in HIV-1 infection
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Citation for published version (APA):
Hazenberg, M. D. (2002). T cell turnover and thymic function in HIV-1 infection
1 Prologue
Reports describing the first patients dying from what was then called gay–related immunodeficiency (GRID) appeared as early as in 1981 (1-3). In the following years, the human immunodeficiency virus type 1 (HIV-1) causing this acquired immunodeficiency syndrome, or AIDS, was isolated (4-5). It became clear that the major characteristic of HIV-1 infection is a gradual loss of CD4\(^+\) T helper lymphocytes from the blood and later from lymphoid tissues, which is associated with deterioration of the immune system, risk for opportunistic infections and malignancies, and eventually death.

Even though the decline of CD4\(^+\) T cell numbers has been long recognized, its exact cause remained unknown for a long time. HIV-1 infects CD4\(^+\) T lymphocytes after binding the membrane receptor CD4. It uses the CD4\(^+\) T cell to produce progeny HIV-1 virions, after which the host cell is killed. Direct infection and killing of CD4\(^+\) T lymphocytes by the virus, however, can account only partly for the observed CD4\(^+\) T cell decline, because per day only about \(10^5\) CD4\(^+\) T cells are productively infected by HIV-1 (6). Assuming that each productively infected T cell is killed, and that the human body contains about \(10^{11}\) CD4\(^+\) T cells, 1% of which resides in the circulation during HIV-1 infection, it would take at least 25 years to lower peripheral blood CD4\(^+\) T cell counts to less than 200 CD4\(^+\) T cells per µl blood or AIDS-defining limits.

Other mechanisms have to be involved, therefore, in HIV-1 related deterioration of the CD4\(^+\) T cell pool. One widely appreciated hypothesis, postulated in 1995, holds that HIV-1 mediated killing of CD4\(^+\) T cells provokes a homeostatic response, such that the immune system is triggered to increase the daily production of CD4\(^+\) T cells to compensate for HIV-1 induced losses. In the end, the immune system in this model was thought to be unable to maintain such high T cell turnover rates (that were estimated to be 70-80 fold increased) and subsequent exhaustion of T cell production was assumed to lead to CD4\(^+\) T cell decline and development of AIDS (7:8). Upon publication of experimental evidence showing that exhaustion by high turnover was rather unlikely (9:10), it was postulated that HIV-1 infection might interfere with the \(de\ novo\) production of T cells by the thymus, leading to CD4\(^+\) T cell depletion (11). In this thesis, both hypotheses are addressed.

References


