Cytomegalovirus-specific T-cell dynamics in HIV infection
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Summary

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Human cytomegalovirus (CMV) is a DNA virus of the β-herpes virus family. Depending on socio-economic circumstances, 50 to 100% of the human population is infected. Although asymptomatic in immunocompetent hosts, CMV infection, reinfection or reactivation can cause serious clinical complications in immunocompromised subjects such as HIV-infected individuals. Cellular immunity is thought to play a crucial role in controlling CMV replication and prevention of disease. The aim of the studies presented in this thesis was to determine immunological factors that may contribute to progression to AIDS with CMV end-organ disease. To this end, dynamics of CMV-specific T-cell responses in terms of number, function and phenotype were analysed in the natural course of HIV-1 infection.

In a longitudinal study, CMV-specific CD8+ and CD4+ T-cell responses were studied in parallel to CMV load in both long-term asymptomatics and progressors to AIDS with or without CMV end-organ disease (chapter 2). In the year before onset of CMV end-organ disease, CMV-specific IFNγ+CD4+ T cells were lost in progressors to AIDS with CMV end-organ disease. Although CMV-specific CD8+ T-cell numbers remained high, only a low proportion produced IFNγ, probably due to insufficient CD4 help. Control of CMV dissemination was lost and CMV load increased sharply. Remarkably, a high proportion of CMV-specific CD8+ T cells expressed perforin and granzyme B. Since we were intrigued by these CMV-specific CD8+ T cells, we continued our studies of these cells in more detail by analysis of a panel of frequently used phenotypical markers (chapter 3). In progressors to AIDS with CMV end-organ disease, highly differentiated CMV-specific CD8+ T cells were detected, which were CD45RO+/−, CD27−, CCR7−, with high CD57 expression and increased Ki67 expression. This phenotype is compatible with effector capabilities, such as killing through perforin and granzyme B mediated-cytotoxicity. Increasing numbers of CMV-infected cells despite the abundance of CMV-specific perforin/granzyme B+ CD8+ T cells suggested that these cells are not protective, but may contribute to tissue-associated immune pathology characteristic for CMV disease.

To try and understand better what role CD4+ T cells might play in progression to disease, function, in terms of IFNγ as well as IL-2, and phenotype of CMV-specific CD4+ T cells were further defined (chapter 5). Interestingly, CMV-specific IFNγ-producing CD4+ T cells expressed a CD45RO−CD27− effecter phenotype and shifted towards the highly differentiated CD45RO−CD27+ phenotype during progression towards CMV end-organ disease, while loosing their proliferative capacity and function in terms of both IL-2- and IFNγ. Antigenic presence could play an important role in driving the differentiation and phenotype of the CMV-specific CD4+ T cells towards the fully differentiated phenotype. Especially in HIV infection, where chronic immune activation seems to exhaust immune responses in general, this could play an
important role. Furthermore, CMV-specific class II tetrameric molecules were used for the first time (chapter 4 describes the synthesis of these novel class II tetramers). We were able to detect CMV-specific tetramer$^+$ CD4$^+$ T cells in two long-term asymptomatics and one progressor to AIDS with CMV end-organ disease. Interestingly, tetramer$^+$ CD4$^+$ T-cell numbers decreased during the course of infection in LTA and seemed to “disappear” in the progressor to AIDS-CMV. However, proliferative capacity was lost as well so we cannot draw preliminary conclusions if indeed CD4$^+$ T cells were physically lost.

In addition to the advanced state of differentiation observed in CMV-specific T cells, we analysed the CD4$^+$ T-cell population as a whole to determine what happens to CMV-driven shaping of the immune response as described in HIV-negative CMV-seropositive adults and children (chapter 3). CD4$^+$ T cells with the characteristic CD27 CD28$^-$ phenotype, previously shown to be induced specifically by CMV infection, were found in very high numbers in all HIV$^+$ individuals, and even in higher numbers in individuals progressing to AIDS-CMV. Also the normally rare, fully differentiated CD45RO$^+$CD27$^-$CD4$^+$ subset increased significantly in progressors to AIDS-CMV. Not surprisingly, the suggested CMV-driven shaping of the immune response was clearest in individuals with overt CMV end-organ disease. CMV-driven shaping of the immune response does play a role as well in HIV-infected children with or without continuous CMV shedding (chapter 6). Expansions of the CD45RA$^+$CD27$^-$ effector CD8$^+$ T-cell population correlated with CMV seropositivity and CMV shedding. We investigated CMV-specific IFN$\gamma$-producing T-cell responses in these children in order to define whether this observation was due to an expansion of the CMV-specific CD8$^+$ effector T-cell population. Although CMV-specific IgG and numbers of CD8$^+$ effector T cells progressively increased in children who continuously shedded CMV, their CMV-specific IFN$\gamma$-producing CD8$^+$ T-cell response as well as its CD8$^+$ CD45RO$^+$CD27$^-$ effector subset was diminished compared to non-shedding children. This might well explain the inability to suppress CMV completely as evidenced by the CMV shedding in these children.

In the last chapter (7), we describe a study in which HIV-, EBV- and CMV-specific CD8$^+$ T cells were analysed longitudinally in rapid (i.e. progressors to AIDS) and slow progressors to AIDS (i.e. long-term asymptomatics) in order to compare virus-specific CD8$^+$ T-cell differentiation. Percentages of CMV-specific CD8$^+$ T-cells increased in contrast to HIV- and EBV-specific T-cells. CMV-specific T cells were also more differentiated as reflected by higher fractions of CD27$^-$ and double positive perforin and granzyme B expressing CD8$^+$ T-cells. Although disease progression does influence phenotype and function of virus-specific T cells, it seems likely that CMV is a “special” virus that is very immunogenic and induces strong immune responses.

In conclusion, chronic CMV infection seems to be associated with highly differentiated CMV-specific CD8$^+$ and CD4$^+$ T cells. CMV seems to shape the
immune response in general too. In immunocompromised individuals, differentiation of T cells may be driven further possibly due to repetitive antigen exposure. The antiviral effect of IFNγ seems to play a crucial role. If IFNγ-producing functional CMV-specific CD4+ T cells disappear and CMV-specific IFNγ+CD8+ T cells decrease, CMV replication may no longer be controlled and the virus disseminates. The cytopathic nature of cytomegalovirus as well as high numbers of perforin+granzyme B+ CMV-specific CD8+ T cells may explain severe immunopathology characteristic of CMV end-organ disease.