Influence of CD4+ cell types on HIV-1 infection

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HIV-1 enters a cell through binding to the CD4 molecule expressed on the cell surface and subsequently to a coreceptor which is predominantly CCR5 or CXCR4. A variety of immune cells expressing CD4 and at least one of the coreceptors are therefore susceptible to infection by HIV-1. Transmission to a new host is almost always established by a CCR5-using virus, while CXCR4-using variants often arise later in infection and are associated with accelerated disease progression. Various cell types are infected to variant levels depending (amongst others) on the expression levels of CD4 and coreceptors, phase of the cell cycle and levels of CC-chemokine production (for CCR5 using viruses). Within the CD4+ lymphocyte compartment the central memory cell population is the predominantly infected subset with HIV-1 copy numbers exceeding those of naïve and effector memory CD4+ T cells. CD4+ lymphocytes contain higher HIV-1 copy numbers than monocytes/macrophages and the biological properties of the virions generated from the different cells may also vary. Differences in virus infectivity, cell tropism and glycosylation among virions produced by both cell types have been described. The genetic composition of the viral quasispecies can also differ among CD4+ cell types with differences in viral diversity. Diversity is usually measured through DNA sequencing of the variable regions of the viral envelope gene (env) which encodes for the protein that protrudes from the virion and mediates viral entry. This protein is involved in binding both CD4 and the coreceptor. Specific amino acid positions within and around the variable V3 region as well as patterns of N-linked glycosylation across the entire envelope have been heavily associated with coreceptor usage. Overall amino acid charge has also been shown to influence coreceptor usage with higher V3 charges being associated with a switch from CCR5 towards CXCR4 usage.

In this thesis we have studied how CD4+ cell type influences HIV-1 infection through analyzing the viral envelope. In Chapter 2 we quantified virus infection levels of naïve and memory CD4+ lymphocyte subsets and observed wide variation among cell types as well as between individuals. Predominant infection of a particular cell subset did not influence the genetic appearance of the viral quasispecies within the CD4+ lymphocyte population. All cell subsets contained HIV-1 variants which were genetically indistinguishable from cell-free virus in serum, which was also identified in a patient undergoing a switch in coreceptor usage. These findings emphasize that all studied lymphocyte subsets contribute comparably to HIV-1 infection, including naïve lymphocytes that contain virus variants that are genetically indistinguishable from serum-derived HIV-1. In Chapter 3 we assessed how 2 to 5 weeks of antiretroviral therapy influenced HIV-1 obtained from the same CD4+ lymphocyte subsets. We observed apparent changes in virus diversity within the effector memory subset and a clear increase in V3 charge, while such changes were absent from naïve and central memory compartments. This may indicate that HIV-1 residing in effector memory cells may be more sensitive to therapy than virus from other CD4+ lymphocyte compartments. Chapter 4 describes a cell-line based method to generate HIV-1
primary isolates based on syncytia formation without requiring a CA-p24 ELISA to monitor virus production. By cocultivating HIV-infected patient PBMC with U87. CD4 cells expressing the CCR5 coreceptor, we generated HIV-1 primary isolates circumventing their variation in susceptibility to HIV-1 infection. This easy-to-use method facilitates for more research to be performed in the field and provides a more standardized method for the generation of primary isolates. We successfully applied this assay in Ghana where we also included patients for a study on the influence of Mycobacterium tuberculosis (MTB) on HIV-1 infection (Chapter 5). With the ongoing HIV-1 epidemic in Sub-Saharan Africa, an increasing number of people suffer from malaria or TB on top of their HIV-1 infection. Research into the mechanisms of how these co-infections influence HIV-1 pathogenesis is beginning to emerge and some co-infections result in faster CD4 decline than others. From HIV-1 infected individuals co-infected with MTB, we studied the phenotype of HIV-1 infected cells to shed light on how HIV-1 infection may influence the TB-specific immune response. We observed that certain MTB-specific cell populations were preferentially infected over others and that these cell types differ in their expression profile of effector molecules. Other pathogens such as cytomegalovirus (CMV) raise a different immune response possibly explaining for reduced CD4 cell depletion during HIV-1 infection. The phenotype or function of a cell responding to such a co-infection may therefore influence to what extent it will be infected (and depleted) by HIV-1. We have also described how cell type affects the phenotype of the virions that are produced (Chapter 6). We observed minor to no influence on infectivity for different CD4+ lymphocyte cell types or coreceptor usage patterns. However, we identified that virus produced by macrophages possess a different sensitivity to 2G12 neutralization compared to virus produced by lymphocytes. The ability of HIV-1 to be transmitted via DC-SIGN to CD4+ lymphocytes may also differ according to the cell type HIV-1 is produced by. These findings could be related to a difference in post-translational glycosylation profile of the viral envelope produced by macrophages versus CD4+ lymphocytes. The gp120 envelope of HIV-1 is heavily glycosylated and both DC-SIGN and 2G12 bind carbohydrates on the viral envelope. These differences in biological properties of viruses produced from different cell types may influence HIV-1 pathogenesis. In the final chapter of this thesis we have discussed these and other findings from this thesis in the context of current literature (Chapter 7). We discuss how cell type may influence HIV-1 infection level, virus evolution and phenotype. We further describe the generation of primary isolates and the influence MTB and HIV-1 have on each other. Overall, this thesis contributes to the knowledge as to how cell type influences HIV-1 infection and may thereby aid in combating this infection.