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CHARACTERIZATION OF HIV-1 IN THE CENTRAL NERVOUS SYSTEM DURING SUPPRESSIVE THERAPY

AKADEMISK AVHANDLING

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av

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ABSTRACT

Combination antiretroviral therapy (cART) is effective in suppressing HIV-1 RNA levels below the lower-limit of detection of clinical assays (<20-50 copies/mL) but is not curative and more sensitive assays can detect very low levels of HIV-1 RNA in plasma even after years of suppressive therapy. If treatment is stopped HIV-1 RNA levels soon increase and immunodeficiency continues to develop. This is due to the small amount of virions present in the blood during suppressive therapy that can infect new cells and cause viral rebound if treatment is stopped. These virions are produced by latently infected resting memory CD4+ T-cells that become reactivated. In addition, other cell types may be producing infectious virions during suppressive therapy. This needs to be explored to direct efforts for the eradication of all infected cells capable of producing virions in order to cure HIV-1. Since current HIV-1 therapy is life-long, costly and not without side effects a cure would be valuable from both an individual perspective as well as from a public health perspective. In this thesis we have, using very sensitive techniques for HIV-1 RNA quantification and sequencing, studied if HIV-1 also persists in the central nervous system (CNS) during suppressive therapy.

We first analyzed paired cerebrospinal fluid (CSF) and plasma samples from elite controllers (who maintain plasma HIV-1 RNA levels at <40 copies/mL without cART) since they have been proposed to serve as a model for a functional cure. We found that, using a very sensitive assay that allows for HIV-1 RNA quantification down to less than 1 copy/mL, HIV-1 RNA could be detected at very low levels in both CSF samples and plasma samples. We then studied subjects on suppressive therapy with HIV-1 RNA levels below the lower limit of detection for clinical assays in both CSF and plasma (<40 copies/mL) and found that, using the same sensitive assay, HIV-1 RNA could be detected at very low levels in 17% of CSF samples and in 57% of plasma samples from these subjects. HIV-1 RNA could be detected in the CSF even after 10 years of suppressive therapy and the detection of CSF HIV-1 RNA was correlated to elevated levels of CSF neopterin, a marker for immune activation. We sequenced HIV-1 RNA in CSF and plasma from subjects on suppressive therapy and found a large fraction of replication incompetent hypermutants among the HIV-1 variants in CSF. In addition, we found one subject with genetically distinct variants in the CSF compared to plasma, consistent with virion production by two populations of cells, one possibly in the CNS. We did not see any signs of evolution among the sequences found in CSF during suppressive therapy. In addition, we found that subjects on suppressive therapy who had their ongoing treatment intensified by the addition of the integrase inhibitor, raltegravir, did not reduce CSF HIV-1 RNA levels or CSF immune activation.

In conclusion, HIV-1 can be detected in the CSF even after years of suppressive therapy. The detection of HIV-1 in the CSF is correlated to intrathecal immune activation. The HIV-1 found in the CSF during suppressive therapy might be produced by cells in the CNS that need to be targeted in order to cure HIV-1. Since there are no signs of viral evolution among sequences found in the CSF during suppressive therapy and the CSF HIV-1 RNA levels are not affected by treatment intensification there does not appear to be any ongoing replication in the CNS during suppressive therapy.