Therapeutic immune recovery prevents emergence of CXCR4-tropic HIV-1

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ABSTRACT

In pre-therapy situations CXCR4-tropic HIV variants increase over time and with stage of disease, whereas under therapy CCR5-tropic variants tend to be more prevalent. The study aim was to assess if a reduction of CXCR4-tropic HIV variants is truly achieved by therapy. NGS and tropism analysis of PBMCs was performed longitudinally on 35 patients before and during therapy. In most patients CXCR4-tropic variants diminished or were lost during therapy. CXCR4-tropic HIV is under pressure and may get selectively depleted in the immuno-competent host.

BACKGROUND

In the absence of any therapy CXCR4-tropic HIV is found to increases over time of infection, associated with an accelerated disease progression. More recent analyses during ART show that in most successfully treated patients the situation is quite different: The majority of them harbors solely CCR5-tropic variants in the circulation. As antiretroviral therapy itself could be responsible for reducing CXCR4-tropic HIV-1 this study aimed at following longitudinally by deep sequencing technology the abundance of CXCR4-tropic viral sequences in infected PBMC during suppressive antiretroviral therapy.

METHODS

The Illumina Miseq platform (NGS) was used to obtain deep sequencing results on provirus from purified PBMC of 35 chronically HIV-1 infected patients in the Swiss HIV Cohort Study prior to and during periods of complete virologic suppression. Virus was permanently suppressed, without any recorded blips, throughout the study time, and for all patients a good simultaneous CD4 T cell recovery has been recorded. All calculations were performed using MEGA 6.0.

RESULTS

In 28 of the 35 patients (80%) of this study we observed that frequencies of CXCR4-tropic provirus decreased under therapy or, in few, remained stably low over time. This is in contrast to the situation in untreated patients. Only in 7 individuals (20%) the frequency of CXCR4-tropic provirus increased during treatment. In all these latter cases a single viral variant emerged, which was already detectable in the population before therapy initiation. In > 50% of the treated patients a certain proviral sequence evolution was seen; interestingly, however, in no single case this evolution indicated a frequency increase of/towards CXCR4-tropic proviruses.

CONCLUSIONS

• CXCR4-tropic variants decrease during therapy.
• An increase in diversity is driven by CCR5-tropic variants.
• We confirm genetic HIV envelope evolution prior to therapy.
• HIV persistence might be driven directly by proliferation of infected cells.
• A selective pressure on CXCR4-tropic variants may support the idea of early therapy initiation in the clinics.

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