Minority quasispecies of drug-resistant HIV-1: Emergence, transmission, dynamics, and clinical relevance in acute and chronic HIV-1 infection.

Summary / Zusammenfassung

1. Summary

Current antiretroviral therapy (ART) has significantly reduced the mortality of human immunodeficiency virus type 1 (HIV-1) infected patients, however, one of the major obstacles in the fight against HIV-1 is the selection of drug-resistant viruses and subsequent therapy failure. New technologies quantifying minority quasispecies of drug-resistant viruses to levels below 1% allow deeper insights into the viral heterogeneity during HIV-1 infection and will be used within this proposed project to determine the impact of virus diversity and quasispecies dynamics on selection, persistence, and transmission of drug-resistant viruses.

Aim 1: Determination of the transmission rate and the persistence of minority quasispecies of drug-resistant HIV-1

In two independent patient cohorts from Switzerland and Germany, we have shown that minority quasispecies of drug-resistant HIV-1, undetectable by conventional population sequencing, can be frequently detected in patients with primary HIV-1 infection (PHI) using highly sensitive allele-specific real-time PCR (AS-PCR). Thus, the transmission rate seems likely to be underestimated when solely based on population sequencing. We will continue with and broaden this study including further patients of the Zurich-PHI-study group, expanding the amount of mutations detected by AS-PCR, and including control groups, for instance, chronically HIV-1 infected patients. This will enable us to determine whether the detection of minority quasispecies of drug-resistant viruses is due to transmission or sporadic appearance. In addition, we will investigate the persistence of those minority quasispecies by measuring their reappearance after treatment interruption of successful ART.

Aim 2: Impact of the prevalence of minority quasispecies of drug-resistant HIV-1 on ART

Treatment decisions based on the genotype of HIV-1 obtained by conventional population sequencing is beneficial for the patient, thus, avoiding the administration of inefficient drugs in case drug-resistant viruses are detectable. It still remains unsolved whether the prevalence of minority quasispecies of drug-resistant viruses also impair the outcome of ART. Thus, we will analyze the clinical response to ART in regard to the prevalence of minority quasispecies of drug-resistant HIV-1 at baseline in the long-term follow-up of primary and chronically HIV-1 infected patients.

Aim 3: Identification of the mechanisms of early selection of drug-resistant HIV-1 during the initial phase of ART and their cellular origin

We have recently shown that drug-resistant viruses can be selected and replicate even in the first months of suppressive ART in treatment-naïve patients suggesting that current ART is not efficient enough to completely block viral replication in all cases. We will use such rapid evolution at sites that confer drug resistance as a marker to identify cell populations in which drug-resistant viruses predominantly arise. For this approach, we will apply a novel technology to isolate plasma virus originating specifically from certain cell populations using magnetically labeled antibodies against cell surface markers which are incorporated in the virus membrane and are specific for certain cellular compartments in longitudinal blood samples of patients during the first months of ART. Those virus populations will be further analyzed using AS-PCR and high-throughput ultra-deep sequencing. Furthermore, the impact of the viral DNA-editing enzyme APOBEC-3G on the evolution of HIV-1 will be investigated. Here, we will compare the rate of G-to-A mutations.
within the genome of HIV-1 in times with and without the selective pressure of ART.

In conclusion, this project will help to elucidate the to date still insufficiently understood relevance of minority quasispecies of drug-resistant HIV-1. An optimal clinical set up combined with the latest molecular technologies will help to unravel critical questions in this research field. In particular, the approach proposed will lead to a definite answer to what extent minority quasispecies of drug-resistant viruses are actually transmitted or do emerge de novo early after primary infection. Furthermore, mechanisms of dynamics and potential differences in cellular reservoirs with regard to the emergence of drug-resistant HIV-1 quasispecies will provide important insights into the pathogenicity of HIV-1 which will finally lead to better understanding of the occurrence of HIV-1 drug resistance. This knowledge will help to refine and improve currently available diagnostic tools to detect HIV-1 drug resistance and will further lead to optimization of long-term antiretroviral treatment strategies.

Weitere Informationen unter http://www.projectdb.snf.ch/webforms/frameset.aspx

Keywords / Suchbegriffe
HIV-1, primary infection, genetic diversity, quasispecies dynamics, minority quasispecies, selection and persistence of drug-resistant viruses, transmission, antiretroviral therapy

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