Translational Genomics of HIV-1 Subtype C in India: Molecular Phylogeny and Drug Resistance

Academic Thesis

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SUMMARY

This thesis describes the translational genomics of HIV-1 subtype C in India from its origin to therapeutic response with the aim to improve our knowledge for better therapeutic and preventive strategies to combat HIV/AIDS. In a systemic approach we identified the molecular phylogeny of HIV-1 subtypes circulating in India and the time to most recent common ancestors (tMRCA) of predominant HIV-1 subtype C strains. Additionally, this thesis also studied drug resistance mutations in children, adolescents and adults, the role of host factors in evolution of drug resistance, and population dynamics of viremia and viral co-receptor tropism in perinatal transmission. Finally, the long term therapeutic responses on Indian national first-line antiretroviral therapy were also studied.

In Paper I, we reported an increase in the HIV-1 recombinant forms in the HIV-1 epidemiology using a robust subtyping methodology. While the study confirmed HIV-1 subtype C as a dominant subtype, its origin was dated back to the early 1970s from a single or few genetically related strains from South Africa whereafter it has evolved independently. In Paper II, the lethal hypermutations due to the activity of human apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3G (hA3G) was significantly associated with antiretroviral therapy (ART) failure in Indian HIV-1 subtype C patients. The presence of M184I and M230I mutations were observed due to the editing of hA3G in the proviral compartment but stop codons were also found in the open reading frames and the same drug resistance mutations were absent in plasma virus. Therefore, it is unlikely that the viral variants which exhibit hypermutated sequences and M184I and/or M230I will mature and expand in vivo and hence are unlikely to have any clinical significance. The high concordance of drug resistance genotyping in the plasma and proviral compartments in therapy-naïve patients, gives weight to the idea of using whole blood for surveillance of drug resistance mutations which precludes logistic challenges of cold chain transport.

In Papers III and IV, we identified a substantial proportion of HIV-1 subtype C perinatally-infected older children who had a high burden of plasma viremia but also had high CD4+ T-cell counts. In addition, older children with HIV-1 subtype C infection presented a high prevalence of predicted X4 and R5/X4 tropic strains which indicates that HIV-1 subtype C strains required longer duration of infection and greater disease progression to co-receptor transition from R5- to X4-tropic strains (IV). Our studies also indicate that transmitted drug resistance is low among Indian HIV-1 infected children, adolescents and adults (II and III).

In Paper V, in a longitudinal cohort study, a good long-term response to the Indian national first-line therapy for a median of nearly four years with 2.8% viral failure, indicating the overall success of the Indian ART program. Our study also showed that three immunologically well patients with virological rebound and major viral drug resistance mutations (M184V, K103N and Y181C) during one study visit had undetectable viral load at their next visit. These findings suggest that use of multiple parameters like patients' immunological (CD4+ T-cell count), virological (viral load) and drug resistance data should all be used to optimize the treatment switch to second line therapy. In conclusion, this translational genomics study enhances our knowledge about the HIV-1 subtype C strains circulating in India which are genetically distinct from prototype African subtype C strains. Considerably more research using appropriate models need to be performed to understand the phenotypic and biological characteristics of these strains to guide efficient disease intervention and management strategies.

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