Differential impact of APOBEC3-driven mutagenesis on HIV evolution in diverse anatomical compartments

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Background: Previous studies on HIV quasispecies have revealed HIV compartimentalization in various tissues within an infected individual. Such HIV variation is a result of a combination of factors including high replication and mutation rates, recombination and APOBEC3-host selective pressure. So far, little data is available on the impact of APOBEC3-induced Guanosine-to-Adenosine (G-to-A) mutations on viral compartimentalization.

Methods: To evaluate the differential impact of APOBEC3-editing in HIV-1 compartments, we studied the level of G-to-A hypermutation in HIV-1 protease and reverse transcriptase bulk sequences among 30 patients for whom peripheral blood mononuclear cells (PBMCs) and body tissues or fluids were collected on the same day (14 paired PBMCs/Cerebral spinal fluid (CSF); 8 paired PBMCs/renal tissues; 8 paired PBMCs/rectal tissues). Differences in the G-to-A mutation frequencies were analyzed using the Hypermut 2.0 program.

Results: APOBEC3-mediated hypermutation were identified in 35% (11/30) of subjects in at least one viral reservoir. Hypermutated sequences were observed more frequently in viral sanctuaries (Total n=10; CSF, n=6; renal tissue, n=1; rectal tissue n=3) compared with peripheral blood (Total n=5). Accordingly, APOBEC3 editing generated more G-to-A drug-resistance mutations in sanctuaries: 3 patients' CSF (i.e G73S in protease; M184I, M230I in RT) and 2 other patients' rectal tissues (M184I, M230I in RT) while such mutations were absent from paired PBMCs. Conversely, in one patient, hypermutation was observed in PBMCs sequences (including M184I in RT) while not detected in rectal tissue sequences.

Conclusion: APOBEC3-induced mutations observed in peripheral blood may underestimate the overall proportion of hypermutated viruses in the body as these mutations were observed more frequently in sanctuaries compared to PBMCs in our study. This phenomenon reinforces the role of APOBEC3 editing in HIV compartimentalization *in vivo*. The resulting mutations may favor escape to antiretrovirals in these compartments in conjunction with a lower penetration of drugs in some sanctuaries. On the other side, because hypermutated sequences often harbor inactivating mutations, this study suggests that accumulation of defective viruses may be more dominant in sanctuaries than in peripheral blood of patients on effective HAART.