[POSTER]

DNA TARGET SPECIFICITY FOR DEAMINATION BY THE APOBEC3 PROTEINS INFLUENCES THEIR POTENCY FOR HIV-1 GENE INACTIVATION

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APOBEC3 (A3) proteins are host intrinsic restriction factors that hinder retroviral replication and spread. The most potent members of the human A3 family against HIV-1 include APOBEC3D (A3D), APOBEC3F (A3F), APOBEC3G (A3G) and APOBEC3H (A3H). These enzymes mutate cytosines into uracils in the minus-strand viral cDNA during reverse transcription. Deamination by the A3 proteins occurs in a specific DNA context; A3G prefers to mutate 5'CC substrates whereas all other A3 target 5'TC motifs. Intense mutation of proviral DNA causes premature stop codons and protein malfunction resulting in the abortion of a productive infection. However, the viral infectivity factor (Vif) expressed by HIV gradually induces the degradation of A3 proteins as it accumulates over the course of the infection, thereby allowing for the generation of negligible amounts of mutations as A3 protein levels drop. This sublethal mutagenesis is believed to be beneficial for the virus through genetic diversification and emergence of more fit or drug-resistant variants. Here, since the generation of termination codons occurs by deamination opposite to TGG tryptophan (Trp) codons, we investigated how target site specificity of A3 proteins influences their gene inactivation potency. We found that A3G is extremely potent at introducing termination codons independently of the intensity of deamination as long as Trp codons are present in a gene. In contrast, A3F's ability to inactivate gene function is highly dependent on the intensity of mutation rather than the generation of stop codons. In summary, our results support that the sublethal mutational burden produced by A3F, and presumably also by A3D and A3H, is likely to result in HIV-1 genetic diversification that is overall more beneficial for the virus than detrimental.