

RETROVIRUS RESISTANCE TO APOBEC3 RESTRICTION

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All organisms have evolved strategies to restrict the integration of foreign DNA into their genomes. Cytidine deaminases encoded by the APOBEC3 (A3) genes of mammalian cells restrict infection by retroviruses and inhibit transposition of mobile genetic elements. A3G can be incorporated into HIV-1 particles in the producer cell and deaminate the nascent single stranded DNA during reverse transcription in the target cell. To counteract A3G restriction, HIV-1 and several other lentiviruses have evolved Vif proteins, which bind A3G and shunt it into proteasomal degradation. Other retroviruses that do not encode Vif use alternative mechanisms to interfere with A3G packaging or activity. In turn, cells have diversified their repertoire of A3 proteins, each of which could interact with viral components in different ways or interact with a diversity of genomic pathogens. Old world primates (OWP) carry seven active A3 genes clustered on chromosome 22; in contrast, mice and pigs have only one, cows and sheep have two, and horses have six A3 genes. We are characterizing the strategies that different primate retroviruses, such as HTLV and SRV, have evolved to counteract A3G in their natural host cells. HTLV has developed a mechanism, which prevents virion incorporation of A3G from various species. In contrast, SRV does not package A3G of its natural host (macaque), but is less exclusive for A3Gs from other species. To better understand this selectivity, we have analyzed the A3G genes of Old world and New world primates (NWP) by database mining and cloning and sequencing A3 genes and cDNAs. We have identified an A3G pseudogene present in both OWP and NWP genomes; in addition, there are at least 8 additional copies of A3G pseudogenes recently spread through the genomes of New world primates. More importantly, the NWP A3 locus itself shows significant differences from that of OWP, resulting from alternative amplification and rearrangements of individual genes. We have cloned A3G cDNAs from several NWP species and are comparing their activity against New world and Old world primate retroviruses. Additionally, we have sequenced several A3G pseudogenes and are comparing their divergence to that of the active genes to gain a better understanding of the selective pressures exerted on their sequences.