Mechanism of HIV-1 Genome Selection

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HIV-1 replication is dependent on efficient incorporation of viral genomes into assembling virions. RNA elements that promote genome selection have been identified, but the determinants of authentic packaging fidelity and efficiency remain unknown. We recently showed that heterogeneous transcriptional start site usage by HIV-1 produces 5′-capped RNAs beginning with one, two, or three 5′-guanosines (^{Cap}1G, ^{Cap}2G, ^{Cap}3G, respectively) that are either selected for packaging as genomes (^{Cap}1G) or retained in cells as translatable mRNAs (^{Cap}2G/^{Cap}3G). ^{2}H-edited NMR structural studies revealed that the ^{Cap}1G transcript adopts a dimeric multi-hairpin structure that sequesters the cap, inhibits interactions with translation initiation factor eIF4E, and resists decapping. In contrast, the ^{Cap}2G/^{Cap}3G transcripts adopt an alternate structure with an elongated central helix, exposed splice donor residues, and an accessible cap. Extensive remodeling, achieved at the energetic cost of a G-C base pair, explains how a single 5′ guanosine modifies the function of a ~9 kilobase HIV-1 transcript. Finally, using an NMR-directed competitive packaging approach, we show that cap sequestration is an essential determinant of HIV-1 genome packaging, likely preventing cap-dependent capture by the cellular RNA processing and translation machinery.