Kinetic model of high packaging selectivity of the dimeric HIV-1 genomic RNA

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1. Abstract

HIV-1 is known to package its genomic RNA (gRNA) with exceptionally high selectivity leading to over 90% of released virions containing a gRNA dimer, despite the extremely low (<0.1%) fraction of gRNA in the cytoplasm of infected cells. Gag assembly into immature virions happens on the plasma membrane (PM) of infected cells at cytoplasmic Gag levels two orders of magnitude below the Gag concentration required for its assembly in bulk solution. Under such low Gag conditions only infrequent Gag dimers or trimers form on cytoplasmic RNA, while subsequent assembly proceeds on the PM. We propose that the measured binding preference of Gag dimer or trimer for the 5' UTR of HIV-1 gRNA (-fold) provides only the first step of Gag enrichment with gRNA, but is insufficient to account for the high gRNA packaging selectivity. We argue that yet more important contribution to selective packaging comes from the merging of the two gRNA-associated Gag clusters accompanying the gRNA dimerization on PM via one of the two mechanisms. The first mechanism involves gRNA dimerization early in the assembly leading to merging of the small Gag clusters thereby bringing the Gag cluster size above its critical value required for the irreversible virion growth. Alternatively, dominant is the merging of two large Gag clusters leading to faster virion assembly completion on gRNA dimer. Which mechanism is responsible for the selective gRNA packaging is yet unknown. We obtain testable predictions for the gRNA dimer packaging selectivity based on each mechanism and as a function of the rates of the gRNA and Gag synthesis, strength of the Gag-Gag and Gag-PM interactions, cell size, Gag cytoplasmic and PM diffusion rates, gRNA dimerization propensity and the gRNA-Gag binding specificity. Our conclusions are consistent with the experimental data, when available, while novel predictions have yet to be tested.