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HIV-1 Preferentially Targets Genes Regulated by PAF-1 and U2 snRNP for Integration

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Pre-mRNA splicing is coupled with promoter-proximal Pol II pausing and alternative polyadenylation (APA). Splicing inhibitors increase pausing and the use of proximal polyadenylation sites (PAS) in intron rich genes by impairing P-TEFb recruitment, which is a core component of the super elongation complex (SEC). The CFIm complex consisting of CPSF6 and CPSF5 also regulates APA by promoting the use of distal PAS. CPSF6 binds viral capsid (CA) to license HIV-1 intranuclear trafficking and integration targeting. Previously, we showed that HIV-1 preferentially integrates into intron rich, Pol II-paused genes. Based on the interconnections between splicing, pausing, and APA, we hypothesized that APA might play a role in HIV-1 integration targeting. Indeed, in Jurat T cells, APA genes regulated by U2 snRNP contained 24% of integration sites (3x compared to RIC or random integration control; p<1E-5). In contrast, nonregulated genes were targeted similarly to all genes (p< 0.2). Further, paused genes regulated by PAF-1, which is also important for APA and for post-integration viral expression, were preferentially targeted (3.5x RIC; p<1E-5), whereas the reciprocal gene set was preferentially avoided (p<1E-5). To test the role of splicing, we infected Jurkat T cells in the presence of the U2 snRNP inhibitor Pladenolide B (Plad B) or the SEC inhibitor KL-2. Plad B significantly reduced genic integration in PAF-1 paused genes but not in unpaused genes. We defined chromosomes with reduced genic integrations (p<1E-04) as Plad B sensitive chromosomes (PBSC) and the remaining chromosomes as Plad B insensitive chromosomes (PBIC; p<0.02)). KL-2 reduced genic integration significantly for PBSC but not for PBIC, suggesting that splicing targets HIV-1 integration into genes regulated by P-TEFb/SEC. To test the roles of integration targeting cofactors, we mapped sites for CPSF6-defective CA mutant viruses or wild type (WT) HIV-1 in LEDGF/p75 knockout (LKO) cells. PBSC supported significantly less genic integration for CA mutants and for WT virus in LKO cells (p<1E-7). However, while PBIC were significantly less targeted by WT virus in LKO cells, these genes were significantly more targeted by CA mutants (p<1E-7 for both comparisons). Thus, the CPSF6-CA interaction is critical for preferential HIV-1 integration targeting of paused genes and APA genes regulated through P-TEFb/SEC.
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