Retrovirology

BioMed Central

Poster presentation

HIV-1 acetylated integrase is targeted by KAP1 (TRIM28) to inhibit viral integration

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from Frontiers of Retrovirology: Complex retroviruses, retroelements and their hosts
Montpellier, France. 21-23 September 2009

Published: 24 September 2009

Retrovirology 2009, **6**(Suppl 2):P2 doi:10.1186/1742-4690-6-S2-P2

This abstract is available from: http://www.retrovirology.com/content/6/S2/P2

Post-translational modifications, such as acetylation, dynamically modulate the chemical and structural properties of proteins generating new protein-protein interfaces. HIV-1 integrase is acetylated by p300 at three specific lysines located in the carboxy terminal domain. In the attempt to understand how acetylation modifies the integration event, we have searched for cellular cofactors that may specifically require acetylation to bind integrase.

To this aim a tethered catalysis system has been exploited to perform a yeast two-hybrid screening. In this assay an integrase constitutively acetylated by fusion with the HAT catalytic domain of p300, was used as a "bait" to screen a human T-cell cDNA library. One of the identified binding factors was KAP1, which showed a higher affinity to integrase following its acetylation. This affinity was confirmed by either pull down assays and *in vivo* co-immunoprecitation in 293T cells. To evaluate the role of KAP1 during HIV-1 life cycle, infections were performed in HeLa and 293T cells transiently and stably silenced for KAP1. Interestingly, the infectivity was 3-10 fold higher than control cells and the analysis of the DNA forms showed a specific enhancement at the level of integration. In a reciprocal experiment overexpression of KAP1 showed a reduction of infectivity by a 50% decrease in integration.

Since integrase activity is positively regulated by acetylation, we then performed experiments to explore whether KAP1 inhibition of viral integration might correlate with modulation of integrase acetylation levels. We demonstrated that KAP1 binding to acetylated integrase indeed induces integrase deacetylation through HDAC1 complex formation. Finally, HDAC1 complex formation is a requirement for KAP1 viral inhibition since no HIV-1 restriction can be observed in cell silenced for HDAC1.

In conclusion, this study reports that KAP1, recently described to restrict M-MLV infectivity in embryonic stem cells at the level of viral transcription, inhibits HIV-1 through a novel mechanism targeting the integration step.