A new role of the HIV-1 nucleocapsid in the spatiotemporal control of the reverse transcription throughout the virus replication cycle

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Retrovirology

BioMed Central

Poster presentation

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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):P14 doi:10.1186/1742-4690-6-S2-P14

This abstract is available from: http://www.retrovirology.com/content/6/S2/P14

Background

Retroviral nucleocapsid (NC) is multifunctional in that it acts throughout the virus replication cycle via a number of molecular interactions. During the early stage, mature NC molecules extensively interact with the viral genome and reverse transcriptase to chaperone proviral DNA synthesis. At the late stage, NC as part of Gag, selects and dimerizes the genomic RNA, which is thought to start the Gag assembly process in infected cells. Interestingly, the RT reaction appears to be tightly controlled during the late steps of HIV-1 replication since the viral DNA synthesis is completed only after virions infect target cells [1]. How this is regulated is yet poorly understood and we hypothesized that the NC might be involved in the timing of RT. To function, NC needs its two conserved CCHC zinc fingers and the flanking basic residues. Therefore, we investigated their role in the temporal control of the RT.

Results

We undertook a detailed quantitative analysis of the viral nucleic acid production throughout the replication cycle by qPCR and qRT-PCR. We measured the effects of NC zinc finger and basic residue deletions and mutations on the conversion of both the genomic and spliced RNA species into DNA. We discovered that viral particles released from the cells expressing HIV-1 NC mutants, contained a high level of DNA (up to 100-fold as compared with wild-type HIV-1) [2,3]. This unexpected accumulation of DNA in NC mutant virions was also independently reported by Thomas et al [4]. Furthermore, we reported for the first time that intravirion DNA presence did not result from natural endogenous reverse transcriptase activity (NERT), but rather from the activation of the RT in the virus producer cells [2,3].

Conclusion

These results provide the first example of RT during the late steps of HIV-1 replication and could bring an alternative explanation for the presence of viral DNA in HIV-1 particles isolated from the peripheral blood and semen of HIV-1-infected patients [5]. The occurrence of late RT inside producer cells is also a property of the foamy viruses that release viral DNA-containing particles and whose Gag domain naturally lacks NC zinc-fingers. It is of great interest to determine whether such timing RT control is a characteristic of the HIV-1 NC or rather a common characteristic among all retroviruses. These investigations are in progress.

Last, these new findings on the role of HIV-1 NC emphasize the fact that the conserved zinc-finger motifs should be viewed as a major target for new drugs against HIV-1.

Acknowledgements

This work was supported by grants from ANRS, SIDACTION and CNRS. YB was supported by RTRS, LH by SIDACTION , and LD by ANRS. We thank Emilie Dumas for support of our current investigation.

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