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Nuclear organization and the regulation of HIV-1 gene expression

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Regulation of gene expression is profoundly involved in HIV-1 pathogenesis. This retrovirus integrates into host chromatin in order to transcribe and replicate it's genome. Lymphocytes harboring a quiescent but inducible provirus are a challenge to viral eradication in infected patients undergoing antiviral therapy. Therefore our understanding of the contribution of sub-nuclear positioning to viral gene expression may have far reaching implications also in the pathology of the infection.

In order to gain insight in the conformation of chromatin at the site of HIV-1 integration we investigated lymphocytes carrying a single latent provirus. In the silenced state the provirus was consistently found at the nuclear periphery, associated in *trans* to pericentromeric heterochromatin in a significant number of quiescent cells. After induction of transcription, this association was lost, although the location of the transcribing provirus remained peripheral. These results unveil a novel mechanism of transcriptional silencing involved in HIV-1 post-transcriptional latency and reinforce the notion that gene transcription may occur also at the nuclear periphery.

However, transcription is not the only limiting process during viral gene expression. Both unspliced and spliced viral RNAs need to be exported for efficient viral replication. In particular unspliced viral RNAs are retained in the nucleus until the viral Rev proteins mediate their export. Both RNA binding proteins and RNA hyperediting by adenosine deamination have been involved in the process of nuclear retention. In order to gain insights into this still poorly characterized pathway, we explored the proteome associated with the unspliced HIV-1 RNAs that are retained in the nucleus. We show that the viral RNA is associated with the host factors PSF/p54^{nrb} and MATR3. PSF/p54^{nrb} bind the viral RNA co-transcriptionally but MATR3 defines a subnuclear compartment where the viral RNA is delivered. Through this pathway, Rev is able to associate with unspliced HIV RNA directing its nuclear export. Interestingly PSF/p54^{nrb} binding and localization to MATR3 foci occur independently of RNA hyperediting. Our findings reveal a novel cellular mechanism of nuclear retention that is hijacked by a virus.