RETROVIROLOGY

ORAL PRESENTATION Open Access

CpG methylation controls reactivation of HIV from latency

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From 16th International Symposium on HIV and Emerging Infectious Diseases
Marseille, France. 24-26 March 2010

Background

DNA methylation of retroviral promoter and enhancer localized in the provirus 5' long terminal repeat (LTR) is considered to be a mechanism of transcriptional suppression that allows retroviruses to evade host immune responses and antiretroviral drugs. However, the role of DNA methylation in the control of HIV-1 latency has never been unambiguously demonstrated, in contrast to the apparent importance of transcriptional interference and chromatin structure, and has never been studied in HIV-1-infected patients.

Methods

We analyzed the relation of latent and reactivated HIV-1 promoters in a model of Jurkat cell lines and in memory $CD4^+$ T cells of long-term aviremic patients by means of bisulfit sequencing and chromatin immunoprecipitation in cell-sorted populations. To assess the resistance of latent HIV-1 to reactivation we exposed the cells to TNF-α, protein kinase C agonists, inhibitors of HDAC, and inhibitors of DNA methyltransferases.

Results

We show in an in vitro model of reactivable latency and in a latent reservoir of HIV-1-infected patients that CpG methylation of the HIV-1 5' LTR is an additional epigenetic restriction mechanism, which controls resistance of latent HIV-1 to reactivation signals and thus determines the stability of the HIV-1 latency. CpG methylation acts as a late event during establishment of HIV-1 latency and is not required for the initial provirus silencing. Indeed, the latent reservoir of some aviremic patients contained high proportions of the non-methylated 5' LTR. In the latent reservoir of HIV-1-infected individuals without detectable plasma viremia, we found HIV-1 promoters and enhancers to be hypermethylated and resistant to reactivation, as opposed to the hypomethylated 5' LTR in viremic patients. However, even dense methylation of the HIV-1 5'LTR did not confer complete resistance to reactivation of latent HIV-1 with some histone deacetylase inhibitors, protein kinase C agonists, TNF-α, and their combinations with 5-aza-2deoxycytidine: The densely methylated HIV-1 promoter was most efficiently reactivated in virtual absence of T cell activation by suberoylanilide hydroxamic acid.

Discussion

The latency controlled solely by transcriptional interference and by chromatin-dependent mechanisms in the absence of significant promoter DNA methylation tends to be leaky and easily reactivable. Tight but incomplete control of HIV-1 latency by CpG methylation might have important implications for strategies aimed at eradicating HIV-1 infection.

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Published: 11 May 2010

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doi:10.1186/1742-4690-7-S1-O8
Cite this article as: Blazkova *et al.*: CpG methylation controls reactivation of HIV from latency. *Retrovirology* 2010 7(Suppl 1):O8.