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Molecular mechanisms involved in HIV latency and implications for HIV treatment and eradication

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Aim

The aim of this presentation is to review the molecular mechanisms necessary for the establishment of HIV-1 latency, their relationship with different cellular and anatomic reservoirs, as well as the current treatment strategies targeting viral persistence in latent reservoirs, their main limitations and future perspectives

Methods

For years, the molecular mechanisms leading to HIV-1 reactivation have been characterised in detail but the study of latency has remained elusive due to the technical limitations that arise when a negative phenomenon, like the absence of replication, is studied. Development of new techniques for studying HIV-1 latency, the identification of factors that restrict retroviral infections, the characterisation of chromatin structure in the setting of viral integration, and the discovery of new systems regulating gene expression

Results

Resting lymphocytes represent an extremely restrictive environment for HIV-1 replication. In contrast, immune activation of CD_4^+ T lymphocytes provides an optimal context for robust HIV-1 replication. Most mechanisms to maintain HIV-1 latency operate at transcriptional level such as the chromosome environment at the site of integration or the availability of viral and host transcription factors. In addition, HIV-1 integration and expression can be restrained or enhanced by different host cell factors such as IkBa, COMMD1, APOBEC3G, LEDGF and Emerin. Finally, both cellular and viral miRNAs could be involved in maintaining HIV-1 latency or in controlling low-ongoing viral replication. Identification of new cellular elements restricting the viral cycle provides a new paradigm on HIV-1 latency.

Discussion

As a lentivirus, HIV-1 is able to infect resting, non-dividing cells where the viral genome can be permanently integrated into the host cell chromosomes. Latent HIV-1 reservoirs are established early during primary infection in lymphocytes and macrophages and constitute a major barrier to eradication even in the presence of highly active antiretroviral therapy (HAART). HIV-1 latency should no longer be considered a merely passive event due to the lack of positive factors but as an active process that is maintained by cellular elements that regulate the gene expression program in the infected cell.

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