New Target for HIV-1 Transcription, CDK11

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The pandemic form of HIV-1 has infected more than 60 million people and caused more than 25 million deaths. Antiretroviral therapy has reduced mortality of AIDS-related deaths, but still there are no effective vaccines or cure. Hence AIDS will continue to be a significant public health threat. HIV-1 must interact with a lot of host proteins to replicate in infected cells. Once in the host, virus persists lifelong, systematically destroying the immune system, which leads to the acquired immunodeficiency syndrome (AIDS). How HIV-1 expresses its genes after integration, which mechanism establish latency during HAART? HIV-1 latency is a reversible state of infected cells where low or absent viral replication is observed together with highly active antiretroviral therapy (HAART). Once therapy is interrupted, viral replication resumes rapidly. Studies in infected cells demonstrated that transcription of the full-length viral genome does not occur. Rather short abortive transcripts from either LTR are observed. These and antisense transcript also mark transcriptional interference. HIV-1 latency is complicated process and depends on many factors. However, in many cells, HIV-1 can be reactivated by different approaches. In the presence of HAART, there is hope that the virus could thus be eliminated from the body. For productive viral transcription to occur, host cell transcription factors (NF-kB), CTD kinases (CDK9, CDK11) and the viral transactivator Tat must be activated and engaged on the 5' LTR. Cell transcriptional machineries recruit cyclin dependent kinases for the multiple purposes such is transcription, splicing, capping, polyadenylation and export. Cyclin dependent kinase 11 (CDK11/PITSLRE) has apparent homology to other CDKs. To study the role of CDK11 we used HIV replication as a model. We found that co-expression of CDK11 and HIV-Luc increased significantly luciferase activity, viral RNA and virion production in 293T or HeLaP4 cells. In contrast, depletion of CDK11 inhibited HIV replication. Phosphorylation of serines at positions 2 and 5 of RNA polymerase II CTD by CDK11 was independent of casein kinase 2 (CK2). Increased 3' end formation, cleavage and polyadenylation of HIV transcripts was found in cells that co-expressed CDK11 and HIV-Luc. CDK11 is recruited to genes via theof TREX-THOC. Of interest, resting CD4+ T cells have vanishingly low levels of CDK11, but they increase following T cell activation (aCD3/aCD28, PMA/ionomycin). Thus, levels of P-TEFb and CycL/CDK11 are insufficient in resting cells to support HIV replication. They must be increased for any successful purging strategy, i.e. "shock-and-kill" of cells to eliminate the reservoir of HIV in the host.