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HIV-1 replication changes the function of the PKR activator PACT

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Background

HIV-1 translation is modulated by the activation of the interferon-inducible Protein Kinase R (PKR), which phosphorylates its downstream target, the eukaryotic translation Initiation Factor 2 (eIF2a). Phosphorylated eIF2a blocks translation initiation and consequently viral replication. PKR is not activated in HIV-1-replicating lymphocytes. Inactivated PKR allows high HIV-1 translation and may contribute to HIV-1 persistence in several cell types.

Methods

Peripheral blood mononuclear cells (PBMCs) were infected with HIV-1 molecular clone pNL4-3. Viral kinetics were followed by reverse transcriptase (RT) assay. Expression of viral and cellular proteins were monitored by immunoprecipitation (IP) and western blots.

Results

PKR is transiently induced and activated in PBMCs after HIV-1 infection and dephosphorylated during viral replication. The expression of two double-stranded RNA binding proteins, the RNA adenosine deaminase (ADAR) 1 and the PKR Activator (PACT) is induced during HIV-1 infection. By co-IP of HIV-1-infected lymphocytes with antibodies against PKR, we identified a multiprotein complex, which contains ADAR1 and PACT. PACT is known to activate PKR after a cellular stress. In cells transfected with an HIV-1 molecular clone, PACT unexpectedly inhibited PKR and eIF2a phosphorylation and increased HIV-1 protein expression and virion production. Short hairpin RNAs against PACT decreased HIV-1 protein expression. Furthermore, ADAR1, the TAR RNA binding protein, TRBP, and PACT all inhibit PKR and eIF2a phosphorylation in HIV-1-expressing cells. In the astrocytic cell line U251MG that weakly expresses TRBP, PACT also mediated an increased HIV-1 protein expression and a decreased PKR phosphorylation. Finally, PACT and ADAR1 interact with each other in the absence of RNA, which may mediate the change of PACT function in HIV-1 infected cells.

Conclusions

In contrast to its previously described activity, PACT contributes to PKR dephosphorylation during HIV-1 replication. This activity is in addition to the previously described inhibition of PACT by TRBP [1] and to the direct activity of ADAR1 on PKR [2]. The change in PACT function is likely due to its interaction with ADAR1 but does not exclude the contribution of another HIV-1 component or virally-induced cellular factor. PKR inactivation likely contributes to HIV-1 persistence in several cell types.

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