Background: Estrogen has been shown to display a protective role against HIV/SIV transmission. The effect of estrogen on HIV infection of primary cells has recently been reported, but the mechanism underlying estrogen-mediated protection is not well defined. In this study, we examined the mechanism by which estrogen inhibits HIV infection in primary macrophages.

Methods: Monocyte-derived macrophages (MDMs) were isolated from PBMCs of healthy human donors, and then treated with 17β-estradiol (E2) at different time points during HIV infection. Cells were infected with either replication-defective HIV pseudotyped luciferase reporter viruses for single-cycle infection assays or replication-competent viruses for multiple round infection assays. Level of viral infection was determined by measuring luciferase activity or by quantitating levels of HIV p24 in culture media by ELISA. E2-induced changes in gene expression of IFNs, SAMHD1, and the APOBEC family proteins were examined by RT-PCR analysis.

Results: E2 inhibited HIV replication in MDMs but did not activated PBMCs or CD4+ T cells. Pretreatment of MDMs with E2 for 24 h was required to block HIV infection. E2 had no effect on HIV infection when MDMs were exposed to virus prior to E2 treatment. Investigation of the mechanism of E2-mediated HIV inhibition revealed E2 did not affect surface expression of CD4 and HIV co-receptors nor HIV attachment. E2 pretreatment also protected MDMs from infection by HIV reporter virus pseudotyped with VSV Env, which can enter cells independent of CD4 and HIV co-receptors. Quantitative PCR analysis of HIV reverse transcribed (RT) products showed E2 blocked the synthesis of late RT products. Investigation into the involvement of host restriction factors in E2-mediated HIV inhibition indicated that E2 induced gene expression of type I IFN and APOBEC3A in MDMs from multiple donors. Importantly, the anti-HIV activity of E2 was abolished in the presence of IFNα neutralizing antibody and was absent in bone marrow-derived macrophages from IFNα receptor deficient mice. Interestingly, HIV exposure suppressed E2-mediated type I IFN induction, suggesting that HIV could antagonize E2-mediated innate immune responses.

Conclusions: IFNα contributed to E2-mediated HIV inhibition in MDMs. E2 blocked HIV infection at the step of late reverse transcription. Induction of IFNα by E2 was associated with an increase in APOBEC3A but not APOBEC3G, APOBEC3F or SAMHD1. HIV can also antagonize E2-mediated type I IFN induction. Our study offers a better understanding of the interplay between HIV and E2-mediated immune responses that will provide insight into an effective strategy for HIV prevention.

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