Anti-HIV-1 Activity of Elafin Is More Potent than Its Precursor's, Trappin-2, in Genital Epithelial Cells

Abstract:

Cervicovaginal lavage fluid (CVL) is a natural source of anti-HIV-1 factors; however, molecular characterization of the anti-HIV-1 activity of CVL remains elusive. In this study, we confirmed that CVLs from HIV-1-resistant (HIV-R) compared to HIV-1-susceptible (HIV-S) commercial sex workers (CSWs) contain significantly larger amounts of serine antiprotease trappin-2 (Tr) and its processed form, elafin (E). We assessed anti-HIV-1 activity of CVLs of CSWs and recombinant E and Tr on genital epithelial cells (ECs) that possess (TZM-bl) or lack (HEC-1A) canonical HIV-1 receptors. Our results showed that immunodepletion of 30% of Tr/E from CVL accounted for up to 60% of total anti-HIV-1 activity of CVL. Knockdown of endogenous Tr/E in HEC-1A cells resulted in significantly increased shedding of infectious R5 and X4 HIV-1. Pretreatment of R5, but not X4 HIV-1, with either Tr or E led to inhibition of HIV-1 infection of TZM-bl cells. Interestingly, when either HIV-1 or cells lacking canonical HIV-1 receptors were pretreated with Tr or E, HIV-1 attachment and transcytosis were significantly reduced, and decreased attachment was not associated with altered expression of syndecan-1 or CXCR4. Determination of 50% inhibitory concentrations (IC50) of Tr and E anti-HIV-1 activity indicated that E is ~130 times more potent than its precursor, Tr, despite their equipotent antiprotease activities. This study provides the first experimental evidence that (i) Tr and E are among the principal anti-HIV-1 molecules of CVL; (ii) Tr and E affect cell attachment and transcytosis of HIV-1; (iii) E is more efficient than Tr regarding anti-HIV-1 activity; and (iv) the anti-HIV-1 effect of Tr and E is contextual.