ABSTRACT

The antiviral role of TRIM E3 ligases *in vivo* is not fully understood. To test the hypothesis that TRIM5α and TRIM22 have differential transcriptional regulation and distinct anti-HIV roles according to infection phase and compartment, we measured TRIM5α, TRIM22 and type 1 interferon (IFN-1)-inducible MxA levels in peripheral blood mononuclear cells (PBMCs) during primary and chronic HIV-1 infection, and in matched PBMCs and central nervous system (CNS)-derived cells. Associations with biomarkers of disease progression were explored. The impact of IFN-1, select pro-inflammatory cytokines and HIV on TRIM E3 ligase-specific expression was investigated. PBMCs from individuals with primary and chronic HIV-1 infection had significantly higher levels of MxA and TRIM22 compared to HIV-1 negative PBMCs ($P < 0.05$, all comparisons). PBMCs from chronic infection had lower levels of TRIM5α compared to primary infection or HIV-1 uninfected (both $P = 0.0001$). In matched CNS-derived samples and PBMCs, higher levels of MxA ($P = 0.001$) and TRIM5α ($P = 0.0001$) were noted in the CNS. There was negative correlation between TRIM22 levels in PBMC and plasma viral load ($r = -0.40$, $P = 0.04$). *In vitro*, IFN-1 and rarely pro-inflammatory cytokines induced TRIM5α and TRIM22 in cell type-dependent manner and knockdown of either protein in CD4+ lymphocytes resulted in increased HIV-1 infection. These data suggest that there are infection-phase specific and anatomically compartmentalized differences in TRIM5α and TRIM22 regulation involving primarily IFN-1 and specific cell types, and indicate subtle differences in the antiviral role and transcriptional regulation of TRIM E3 ligases *in vivo*.

Importance Interferon type I-inducible TRIM E3 ligases are a family of intracellular proteins with potent antiviral activities mediated through diverse mechanisms. However, little is known about the contribution of these proteins to antiviral immunity *in vivo* and how their expression is regulated. We show here that TRIM5α and TRIM22, two prominent members of the family, have different expression patterns *in vivo* and that expression pattern depends on HIV-1 infection status and phase. Furthermore, expression differs in peripheral blood versus central nervous system anatomical sites of infection. Only TRIM22 expression correlates negatively with HIV-1 viral load but gene silencing of both proteins enhances HIV-1 infection of target cells. We report on subtle differences in TRIM5α and TRIM22 gene induction by IFN-1 and pro-inflammatory cytokines in CD4+ lymphocytes, monocytes and neuronal cells. This study enhances our understanding of antiviral immunity by intrinsic antiviral factors and how their expression is determined.