EuroSciCon

EuroSciCon Conference on
Virology and Infectious Diseases

April 22-23, 2019
Athens, Greece

Arch Clin Microbiol 2019, Volume:10
DOI: 10.4172/1989-8436-C1-018

HIV-1 VPR TARGETS TET2 FOR DEGRADATION BY CRL4VPRBP E3 LIGASE TO SUSTAIN IL-6 EXPRESSION AND ENHANCE HIV-1 PATHOGENESIS

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HIV-1 expresses several accessory proteins to counteract host anti-viral restriction factors to facilitate viral replication and disease progression. One such protein, Vpr, has been implicated in affecting multiple cellular processes, but its mechanism remains elusive. Here we report that Vpr targets TET2 for polyubiquitylation by the VprBP-DDB1-CUL4-ROC1 E3 ligase and subsequent degradation. Genetic inactivation or Vpr-mediated degradation of TET2 enhances HIV-1 replication and substantially sustained expression of the pro-inflammatory cytokine interleukin-6 (IL-6), correlated with reduced recruitment of histone deacetylase 1 and 2 to and enhanced histone H3 acetylation of the IL-6 promoter during resolution phase. Blocking IL-6 signaling reduced the ability of Vpr to enhance HIV-1 replication. We conclude that HIV-1 Vpr degrades TET2 to sustain IL-6 expression to enhance viral replication and disease progression. These results suggest disrupting the Vpr-TET2-IL6 axis may prove clinically beneficial to reduce both viral replication and inflammation during HIV-1 infection.

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