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Long-term delta-9-tetrahydrocannabinol administration promotes lncRNA *MMP25-AS1*-*MMP25* mRNA interactions to preserve intestinal epithelial barrier function in chronic HIV/SIV infection

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Background: Unresolved chronic intestinal inflammation in HIV-infected individuals on suppressive ART promotes dysbiosis and translocation of microbial products that can systemically reach the brain and induce neuroinflammation/HIV-associated neurocognitive disorders. Since long-term Δ^9 -tetrahydrocannabinol (Δ^9 -THC) administration reduced intestinal inflammation in SIV-infected rhesus macaques (RMs), we hypothesized that modulation of long non-coding RNA (lncRNA) expression represents epigenetic mechanisms underlying its intestinal epithelial protective effects. **Methods:** Using microarray, we profiled lncRNA and mRNA expression in colonic epithelium (CE) of uninfected (n=6) and SIV-infected RMs administered either vehicle (VEH/SIV; n=5) or Δ^9 -THC (THC/SIV; n=6). **Results:** Relative to controls, fewer lncRNAs were up/downregulated in CE of THC/SIV compared to VEH/SIV RMs. Interestingly, several lncRNAs associated with inflammation; *MALAT 1*, *GATA6-AS1*, *GATA3-AS1*, *SPRY-IT1* were exclusively upregulated in CE of VEH/SIV RMs. More importantly, natural antisense lncRNA *MMP25-AS1* was significantly upregulated (FC=2.3) in the CE of THC/SIV RMs while its associated protein coding gene *MMP25* (maintains proinflammatory state in intestine, responds to translocating luminal LPS, immune activation) was significantly downregulated (FC = 2.2). LncTAR analysis confirmed two significant homology regions and an energetically stable (nDG=0.2626) mRNA-lncRNA duplex structure between *MMP25* and *MMP25-AS1*. Immunohistochemistry confirmed significantly elevated MMP25 protein expression in CE of VEH/SIV compared to THC/SIV RMs. Overexpression and RNA pull-down experiments confirmed the ability of *MMP25-AS1* to directly bind MMP25 and significantly reduce its mRNA and protein expression. **Conclusions:** Our data suggests that *MMP25-AS1* is a negative regulator of *MMP25* and low-dose THC can epigenetically suppress *MMP25* mRNA/protein expression through upregulation of its natural antisense *MMP25-AS1* expression.