Long-term delta-9-tetrahydrocannabinol administration promotes IncRNA **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.