Differential Effects of CB2 Agonism on HIV Replication and Inflammatory Activation in Myeloid Cells

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BACKGROUND

HIV productively infects cells that express both CD4 and CCR5 or CXCR4, including brain-resident macrophages and microglia, which can drive inflammation and provide a persistent viral reservoir in the central nervous system.

Chronic neuroinflammation associated with HIV infection remains persistent despite effective antiretroviral therapy.

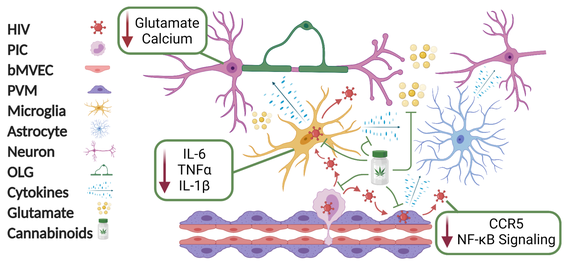
Endogenous and exogenous cannabinoids can act as modulators of neurotransmitter release and inflammatory activation, two mechanisms implicated in HIV-associated neuropathogenesis.

Selectively targeting the primary cannabinoid receptor on immune cells, cannabinoid receptor 2 (CB2), offers an opportunity to modulate HIV replication and inflammation in the CNS without CB1-mediated psychoactive effects.

METHODS

In primary human monocyte-derived macrophages (hMDM) and human induced pluripotent stem cell-derived microglia (iMg), changes in gene expression and cytokine/chemokine secretion following infection with HIV_{ADA} were evaluated using RNA sequencing and Bio-Plex® 48-Plex Pro Human Cytokine Screening Panel, respectively.

The CB2-specific JWH-133, a synthetic cannabinoid (Ki, 3.4 nM; >200-fold selectivity for CB2 over CB1) and the CB2-specific, SR-144,528, a CB2-selective inverse agonist (Ki, 0.6 nM; >600-fold selectivity for CB2 over CB1) were used to interrogate the role of CB2 agonism on the modulation of HIV replication and inflammation in hMDM and iMg.



Modified from Starr, Jordan-Sciutto, and Mironets. *Viruses* (2021)

While their shared myeloid lineage suggests functional overlap, macrophage and microglia susceptibility to HIV infection, cytokine secretion, and transcriptomic responses differ as do their responses to CB2 signaling.

Careful dosing and targeted delivery should be considered to harness the therapeutic utility of CB2 agonism, to avoid overdosing microglia while maintaining desired effects in macrophages

RESULTS

Figure 1. CB2 agonists dose-dependently reduce HIV replication in macrophages and microglia

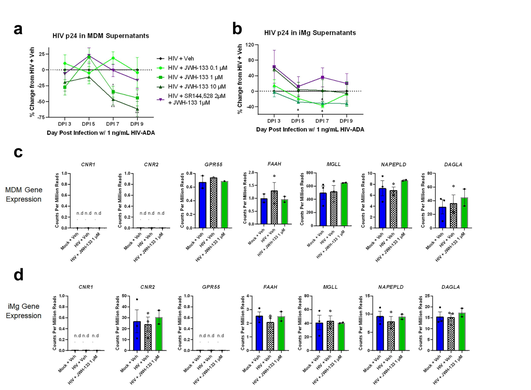


Figure 2. CB2 activation reduces the number of infected cells without altering HIV receptor expression

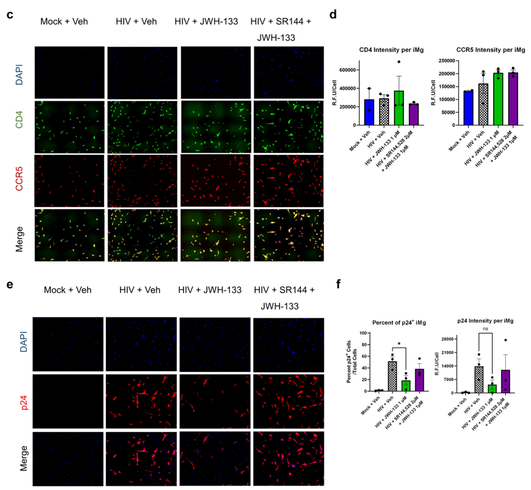


Figure 3. CB2 agonists reduce global cytokine release following HIV infection in MDMs but not in iMg

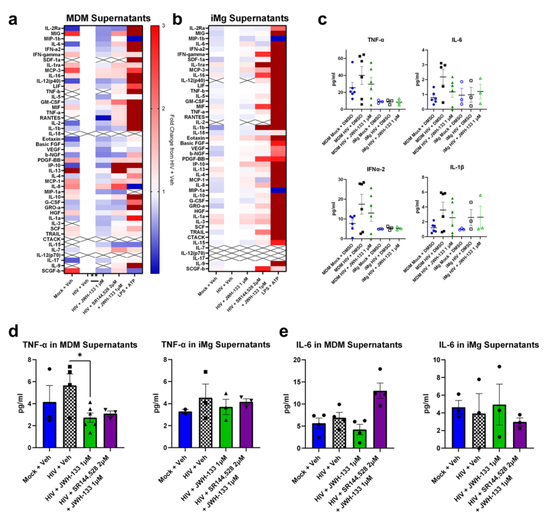


Figure 4. In iMg, CB2-specific agonists impair HIV-induced NLRP3 inflammasome activation with a corresponding increase in autophagosome number

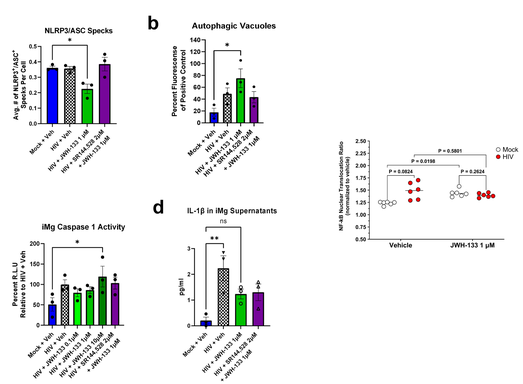
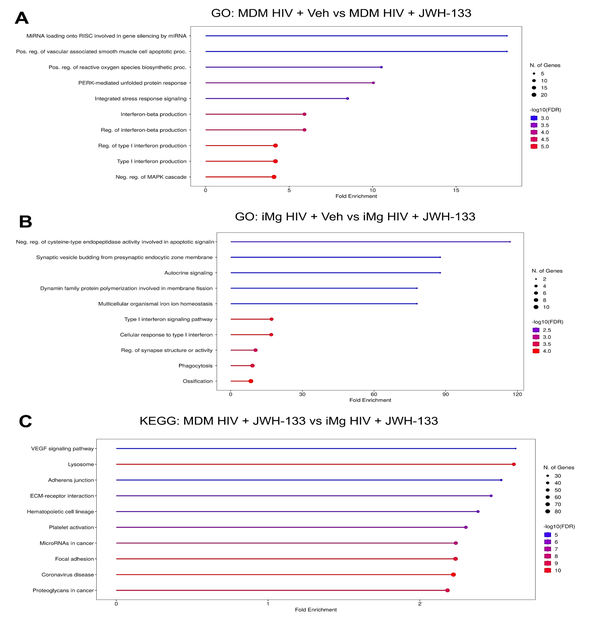


Figure 5. RNA-seq identifies convergent and divergent responses to CB2 signaling between HIV-infected MDMs and iMg



CONCLUSIONS

- This study identifies key differences in CB2 response between myeloid lineage cell types and implicates CB2-specific agonists as promising candidates for the regulation of HIV-associated neuroinflammation.
- While their shared myeloid lineage suggests functional overlap, our results indicate macrophage and microglia susceptibility to HIV infection, cytokine secretion, and transcriptomic responses differ as do their responses to CB2 signaling.
- Although general trends were shared between the two cell types, careful dosing, and perhaps even targeted delivery, should be used in future in vivo studies exploring the therapeutic utility of CB2 agonism, to avoid overdosing microglia while maintaining desired effects in macrophages.

ADDITIONAL KEY INFORMATION

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