TLR7 Agonist GS-9620 Activates HIV-1 in PBMCs from HIV-Infected Patients on cART

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Overview

The pharmacological activation of TLR7 has been considered to be a key part of the strategy towards reactivating latent HIV-1 in infected patients. GS-9620 is a selective TLR7 agonist currently being evaluated in patients with chronic hepatitis B (Whitney et al., J Hepatol 2015). The present study explores the effect of GS-9620 on HIV activation in PBMCs from HIV-infected patients on cART.

Methods

• HIV-1 infected donors on cART (patience HIV RNA <100 copies for >1 yr)
• PBMCs from donors leukapheresis were treated with DMSO or GS-9620 (100 or 1,000 nM) in the presence of HIV-1 (200, 100, 10 nM) for 4 days
• Cytokine/biomarker and cultured supernatants were measured using 38-plex Luminex panel for 3 IFNs and 15 other cytokines/chemokines
• HIV-1 RNA in cell culture supernatants was quantified by real-time qRT-PCR using the AmpliPrep/COBAS® TaqMan® assay

Results

• GS-9620 activated expression of ex vivo PBMCs from HIV-infected patients on cART with prolonged virologic suppression
• GS-9620 (100 – 1,000 nM) induced 2- fold HIV activation in PBMCs from 13/18 (72%) donors with a geometric mean of 8.1-fold activation.
• Donor-dependent variation in HIV activation may be due to combined “kick” and “kill” effects induced by GS-9620
• GS-9620 induced type I IFNs and IFN-inducible cytokines, IFN-α/β receptor signaling was required for maximal activation of HIV by GS-9620
• Recombinant IFNα-2a activated HIV in PBMCs from 3/4 donors. INFα2a did not activate HIV in DC T cells from 2 donors (data not shown)
• Positive correlation was observed between GS-9620- induced peak levels of IFN-α/β and TNF-α and HIV activation levels. The role of these chemokines in the activation of HIV remains to be established
• GS-9620 treatment reduced subsequent response of latent HIV reservoir to PRC agent-mediated activation.

Conclusions

• GS-9620 activated HIV expression in ex vivo PBMCs from HIV-infected patients on cART with prolonged virologic suppression

References

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