PUTTING THE KILL INTO SHOCK AND KILL USING PRO-APOPTOTIC DRUGS WITH LATENCY REVERSING AGENTS

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Background:
One strategy to eliminate latently infected CD4+ T-cells in HIV+ individuals on antiretroviral therapy (ART) is to reactivate virus expression using latency reversing agents (LRAs). However, LRAs alone in clinical trials have not cleared latently infected cells. Thus, additional strategies are needed to kill reactivated cells. Phosphoinositide 3-kinases (PI3K) and Bcl-2 both prevent apoptosis. We hypothesize that combining PI3K or Bcl-2 inhibitors to increase cell sensitivity to apoptosis, with LRAs to drive pro-apoptotic viral protein expression, will selectively clear latently infected cells.

Methods:
The impact of PI3K inhibitors (IPI-4X, IPI-3063, Wortmannin) or Bcl-2 inhibitor (Venetoclax) with LRAs (vorinostat, panobinostat, romidepsin, bryostatin, PMA/PHA) on HIV expression and cell death was evaluated. In the J-Lat6.3 cell-line, we used flow cytometry to quantify HIV LTR-driven green fluorescent protein (GFP) and violet dead stain for cell death. In CD4+ T-cells from HIV+ individuals on ART we quantified HIV RNA and integrated DNA by qPCR.

Results:
In J-Lat6.3, all LRAs increased GFP expression (3.3-1333 fold) but PI3K inhibitors with LRAs did not increase cell death. Using CD4+ T-cells from individuals on ART, in one participant, IPI-4X with romidepsin or PMA/PHA, and Wortmannin with PMA/PHA, reduced HIV DNA 24%-27% versus DMSO control. In another participant, IPI-4X and Wortmannin alone reduced HIV DNA 26%-32%, which increased to a 36%-44% decline when combined with RMD or PMA/PHA. Venetoclax alone decreased HIV DNA in both participants (28% and 47%), which was not increased by adding RMD or PMA/PHA.

Conclusion:
PI3K inhibitors combined with LRAs do not enhance apoptosis in the J-Lat6.3 cell-line. A reduction in HIV DNA in CD4+ T-cells was observed ex vivo in two HIV+ individuals on ART using a PI3Ki with an LRA, The combination of PI3Ki and LRAs should be further explored as a strategy to eliminate latency.

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