**ABSTRACT**

Latent HIV reservoirs represent a major barrier to eradication. We propose a novel strategy to eliminate this reservoir using a class of oncolytic viruses (OV) that include Maraba (MG1) and Vescular Stomatitis Virus (VSVΔ51). These recombinant OV target cancer cells by exploiting defects in type I interferon (IFN) signaling. Similar alterations in IFN-mediated antiviral responses are also seen in HIV-infected cells, providing a crucial link between cancer cells and the latent HIV reservoir. We hypothesize that MG1 and VSVΔ51 selectively target and kill latent HIV-infected cells.

Latently HIV-infected myeloid (U1 and OM10.1) cell lines, as well as their respective parental uninfected controls (U937 and HL60) were incubated with GFP-expressing MG1 or VSVΔ51. Productive OV infection was quantified by flow cytometry. PI, MTT, and Alamar Blue assays were used to assess cell viability. Type I IFN response to OV infection was characterized by measuring IFNα secretion by ELISA, as well as by PKR expression by Western blot. OV infection of primary monocytes, MDMs, and CD4+ T cells from HIV-uninfected donors was also assessed.

U1 and OM10.1 cells were significantly more susceptible to MG1 and VSVΔ51 infection and killing than their respective HIV-uninfected U937 and HL60 parental controls. IFNα secretion significantly increased in response to OV infection in control cell lines, but not in the latently HIV-infected cells. In parallel, PKR expression in response to OV infection was significantly higher in the HIV-uninfected controls than in the latently HIV-infected cells. Primary monocytes, MDMs, and CD4+ T cells from HIV-infected individuals were relatively resistant to OV infection and killing.

Latently infected myeloid cells are preferentially targeted and killed by MG1 and VSVΔ51 when compared to their uninfected parent cells. Underlying defects in type I IFN responses in latently HIV-infected cells may facilitate selective targeting by OV. Therefore, our results suggest that the use of OV may represent a novel and potentially safe approach to selective elimination of the latent HIV reservoir.

**RESULTS**

**1. LATENTLY HIV-INFECTED MYELOID CELL LINES, U1 AND OM10.1, ARE PREFERENTIALLY TARGETED BY MG1 AND VSVΔ51**

- **A.** Representative contour plot following infection and PI staining. B. LDL-R expression on U937 and U1 cells (n=5). C. Effect of increasing doses of MG1 virus on GFP expression and cell viability in U937 and U1 cells at 20h post-infection (n=8).

- **B.** Effect of increasing doses of VSVΔ51 virus on GFP expression and cell viability in U937 and U1 cells at 24h post-infection (n=5). *P<0.05; **P<0.01; ***P<0.001.

**2. DEFECTS IN TYPE I INTERFERON RESPONSE IN LATENTLY INFECTED MYELOID CELLS MAY FACILITATE TARGETING BY OV**

- **A.** Representative contour plot following infection and PI staining. B. LDL-R expression on U937 and U1 cells (n=5). C. Effect of increasing doses of MG1 virus on GFP expression and cell viability in U937 and U1 cells at 20h post-infection (n=8).

- **B.** Effect of increasing doses of VSVΔ51 virus on GFP expression and cell viability in U937 and U1 cells at 24h post-infection (n=5). *P<0.05; **P<0.01; ***P<0.001.

**3. REACTIVATION OF HIV PRODUCTION IN OM10.1 CELLS USING VORINOSTAT ENHANCES OV-MEDIATED INFECTION AND KILLING**

- **A.** Representative contour plot following infection and PI staining. B. LDL-R expression on U937 and U1 cells (n=5). C. Effect of increasing doses of MG1 virus on GFP expression and cell viability in U937 and U1 cells at 20h post-infection (n=8).

- **B.** Effect of increasing doses of VSVΔ51 virus on GFP expression and cell viability in U937 and U1 cells at 24h post-infection (n=5). *P<0.05; **P<0.01; ***P<0.001.

**4. CD4+ T CELLS AND MONOCYTES ARE RESISTANT TO THE CYTOTOXIC EFFECTS OF OV**

- **A.** Representative contour plot following infection and PI staining. B. LDL-R expression on U937 and U1 cells (n=5). C. Effect of increasing doses of MG1 virus on GFP expression and cell viability in U937 and U1 cells at 20h post-infection (n=8).

- **B.** Effect of increasing doses of VSVΔ51 virus on GFP expression and cell viability in U937 and U1 cells at 24h post-infection (n=5). *P<0.05; **P<0.01; ***P<0.001.

**DISCUSSION**

- **MG1 and VSVΔ51 preferentially infect and kill the latently HIV-infected U1 and OM10.1 cells in both a dose- and time-dependent manner.**

- **Reactivation from HIV latency using Vorinostat may represent a viable combinatorial approach as it enhanced HIV infection and killing in OM10.1 cells, as well as resulted in a decrease in total p24 expression.**

- **Defects in Type I IFN pathways identified in these cells may contribute to the observed OV selective targeting.**

- **Primary CD4+T cells and monocytes are resistant to MG1 and VSVΔ51. Therefore, the OV approach may represent a novel and potentially safe approach to selective elimination of the HIV reservoir.**

**Future direction:** Investigating the effects of OV infection in an in vivo model of HIV latency.

**REFERENCES**

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