Targeting HIV persistence during ART (cure strategies)

PE24

MG1 and VSVΔ51 viruses target and kill latently HIV-infected myeloid cells

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Background: 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 Vesicular 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 cells that constitute the HIV reservoir. We hypothesize that MG1 and VSVΔ51 selectively target and kill latently HIV-infected cells.

Methods: Latently HIV-infected myeloid (U1 and OM10.1) cell lines, as well as their respective parental uninfected controls (U937 and HL60) were infected 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 PKR expression by Western blot. OV infection of primary monocytes, MDMs, and CD4+ T cells from HIV-uninfected donors was also assessed.

Results: 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-uninfected individuals were relatively resistant to OV infection and killing.

Conclusions: Latently HIV-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