Targeting HIV persistence during ART (cure strategies)

PE24
MG1 and VSVΔ51 viruses target and kill latently HIV-infected myeloid cells

Ranganath N.1, Côté S.2, Sandstrom T.1, Angel J.2,3
1University of Ottawa, Biochemistry, Microbiology, Immunology, Ottawa, Canada, 2Ottawa Hospital Research Institute, Infectious Disease, Ottawa, Canada, 3The Ottawa Hospital, Infectious Disease, Ottawa, Canada

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.