[ORAL]

MG1 AND VSVΔ51 VIRUSES TARGET AND KILL LATENTLY HIV-INFECTED MYELOID CELLS

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BACKGROUND: Despite effective viral suppression on HAART, latent HIV reservoirs continue to present a major barrier to eradication. We propose a novel strategy to target this reservoir using a class of oncolytic viruses (OV) that include the 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), 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. Viability was assessed by PI, MTT, and Alamar Blue assays. Type I IFN response to OV infection was characterized by measuring IFNα secretion by ELISA and PKR expression by Western blot.

RESULTS: The latently HIV-infected myeloid cell lines U1 and OM10.1 were significantly more susceptible to MG1 and VSVΔ51 infection and viral cytopathic effects than the HIV-uninfected controls in both a dose and time-dependent manner. IFNα secretion in response to OV infection increased significantly in U937 and HL60 controls compared to the latently HIV-infected cells. In addition, PKR expression under basal conditions and in response to OV infection was significantly higher in U937 than in U1 cells.

CONCLUSIONS: Latently HIV-infected myeloid cell lines are preferentially targeted and killed by MG1 and VSVΔ51 when compared to their uninfected parent cells. In parallel, underlying defects in type I IFN response are present in latently HIV-infected cells, which may facilitate selective targeting by OV. Therefore, our results suggest that the use of OV may represent a novel approach to selective elimination of the HIV reservoir.

[POSTER]

HUMAN CD4+ T CELLS, MONOCYTES, AND MONOCYTE DERIVED MACROPHAGES ARE RESISTANT TO INFECTION BY MG1 AND VSV-Δ51

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INTRODUCTION: Complete viral clearance in HIV-infected patients is significantly impeded by the formation of latent HIV reservoirs, which are unresponsive to current therapies. Oncolytic viruses (OVs) are currently being investigated as a novel approach to eliminating the HIV reservoir. However, for this to be a viable treatment option it is imperative that healthy cells are spared from cytopathic effects. Two OVs, Maraba (MG1) and Vesicular Stomatitis Virus (VSV-Δ51), have been designed to preferentially infect cancer cells lacking a robust Type I IFN response. Similar impairment of Type I IFN-mediated antiviral proteins has been described during HIV infection. Thus, we hypothesize that MG1 and VSV-Δ51 will spare healthy cells, while specifically infecting and killing HIV-infected cells.

METHODS: Human CD4+ T cells and monocytes were isolated from healthy donors' blood. CD4+ T cells (unstimulated or PHA/IL-2 stimulated), monocytes, and MDMs were infected with increasing MOIs of GFP-expressing MG1 or VSV-Δ51. At various time points, GFP expression and PI staining were measured by flow cytometry to quantify productive infection and cell viability, respectively. The ability of resting CD4+ T cells to express specific IFN-stimulated genes involved in viral clearance was also investigated. Cells were treated with IFN-α and expression of PKR was assessed by immunoblotting.

RESULTS: Primary monocytes, MDMs, and unstimulated CD4+ T cells were relatively resistant to OV infection and killing. However, PHA/IL-2 treated CD4+ T cells exhibited increased GFP expression in a dose dependent manner. Preliminary results demonstrate a loss in viability during VSV-Δ51, but not MG1 infection. Increased PKR expression following IFN-α treatment in both resting and PHA/IL-2 stimulated CD4+ T cells demonstrated a robust response to exogenous Type I IFN.

CONCLUSION: These results suggest that healthy immune cells are resistant to OV infection and cytopathic effects. Future experiments will investigate both specificity of OV infection and expression of Type I IFN-mediated antiviral proteins during HIV infection. This may lend feasibility to the eradication of the latent HIV reservoir by MG1 or VSV-Δ51 treatment.