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Abstract

Cell Surface-Expressed GPI-Anchored Peptides from the CHR Domain of gp41 Are Potent Inhibitors of HIV-1 Fusion †

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Abstract: Current antiretroviral therapy efficiently suppresses viral replication but cannot eliminate latent HIV reservoirs. Moreover, the associated high costs, side effects, and drug resistance have stimulated a need for the development of alternative methods of HIV-1/AIDS treatment, such as peptide inhibitors or gene editing. Recently, we have developed Surface Oligopeptide knock-in for Rapid Target Selection (SORTS), a method for the rapid selection of CRISPR/Cas9 gene-edited cells via knock-in of the Flag and HA epitope tags embedded into the shortest GPI-protein, CD52. By targeting the capsid region of the HIV-1 genome, we demonstrate that SORTS can be applied in provirus eradication. However, the cells with inactivated provirus will be susceptible to HIV re-infection. We hypothesized that knocking in one of the peptides from the CHR-domain of *gp41*, which are known potent inhibitors of HIV-1 fusion, instead of the epitope tag, will provide "post-curable" HIV-1 resistance. While these peptides were extensively studied as soluble substances, their inhibitory effects on HIV after expression on cell surfaces via GPI-anchor are largely unknown. In this study, we established HEK293T/CD4/R5 and Raji/CD4/R5 HIV-1 permissive cell lines that stably expressed one of the gp41 peptides C34, MT-C34, MT-C34-R, and MT34-15D, or alfa-helix mimetics HP23L, p52, and MT-WQ-IDL. For cell surface delivery, the indicated peptides were embedded into the CD52 molecule, and upstream GFP was used to select transformed cells. Using a single-cycle replication assay with the inLuc reporter vector and different Envs, we demonstrated that C34-based GPI-anchored peptides inhibited both cell-free and cell-to-cell HIV-1 infection by at least two orders of magnitude. With the exception of HP23L, the alfa-helix mimetics were less potent inhibitors. Thus, peptides from gp41 associated with lipid rafts and exerted a strong inhibitory activity which can far exceed that determined for soluble peptides, but this should be tested further.

Keywords: HIV-1; fusion inhibitor peptides; GPI-anchored peptides; gene editing; CD52

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