Virol Mycol 2018, Volume 7
DOI: 10.4172/2161-0517-C2-027

Antibody-dependent cellular cytotoxicity against reactivated HIV-1 latently infected cells

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Current treatments cannot eradicate HIV-1 due to the presence of latently infected cells which harbor transcriptionally silent HIV-1. Antibodies can kill latently infected cells after their activation and subsequent expression of envelope glycoprotein (Env). However, antibodies can neither bind nor neutralize all isolates, thereby allowing virus to escape immune surveillance. We have previously generated a bispecific multivalent molecule (LSEVh-LS) based on one-domain CD4. LSEVh-LS exhibits exceptionally potent and broad neutralizing activity as tested against panel of non-Chinese isolates. In this report, however, we have used a defucosylated variant of LSEVh-LS (LSEVh-LS-F) to enhance its antiviral activity through FcγRIIIa-mediated antibody-dependent cellular cytotoxicity (ADCC). Compared to fucosylated LSEVh-LS, LSEVh-LS-F had higher affinity for FcγRIIIa and was more effective in inducing ADCC to both the wild-type HIV-1-infected cells and the reactivated HIV-1 latently infected ACH2 cells. LSEVh-LS-F was found to be more efficient in inhibiting viral replication and eliminating the reactivated HIV-1-infected CD4+ T cells from patients receiving suppressive highly active anti-retroviral therapy (HAART). It also inhibited all the tested pseudoviruses and primary strains isolated in China with potency about 3~4-fold higher than VRC01. Therefore, LSEVh-LS-F is a promising candidate therapeutic for treating HIV-1 infection and eliminating HIV-1-infected cells, including the reactivated HIV-1 latently infected cells.

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