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CD4 mimetics sensitize HIV-1-infected cells to ADCC

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Background: Prevention of HIV-1 transmission and progression likely requires approaches that can specifically eliminate HIV-1-infected cells. There is increasing evidence supporting a role of Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) in controlling HIV-1 transmission and disease progression. Importantly, the interaction of HIV-1 envelope (Env) glycoproteins with the CD4 receptor was recently reported to be required for efficient exposure of ADCC-mediating Env epitopes. In that context, HIV-1-infected cells presenting HIV-1 Env in the CD4-bound conformation on their surface were found to be preferentially targeted by ADCC-mediating antibodies present in sera of HIV-1-infected individuals. However, HIV-1 has evolved a sophisticated mechanism to avoid exposure of ADCC-mediating Env epitopes by downregulating CD4 and by limiting the overall amount of Env at the cell surface.

Methods: Rationally-designed CD4-mimetic compounds (CD4mc) have been shown to induce thermodynamic changes in HIV-1 Env similar to those induced by CD4 and sensitize HIV-1 particles to neutralization by otherwise non-neutralizing CD4-induced antibodies. In this study, we explored the capacity of such compounds to promote the CD4-bound conformation of Env and thereby sensitize HIV-1-infected cells to ADCC mediated by sera, cervico-vaginal lavages and breast milk from HIV-1-infected individuals, using a FACS-based ADCC assay.

Results: We observed that certain CD4mc induce the CD4-bound conformation of Env and thereby sensitize cells infected with primary HIV-1 isolates to ADCC mediated by prevalent and easy-to-elicit antibodies present in sera from early converters and chronically-infected individuals. Importantly, CD4mc also enhanced recognition and ADCC-mediated elimination of HIV-1-infected cells by antibodies present in breast milk and cervico-vaginal lavages of HIV-1-infected women. Finally, we identified one CD4mc with the capacity to sensitize endogenously-infected ex-vivo-amplified primary CD4 T cells to ADCC killing mediated by autologous sera and effector cells.

Conclusions: By pushing Env into the CD4-bound conformation, CD4mc might represent an alternative and/or complementary approach to currently-available drugs for preventing viral transmission and might represent a new strategy aimed at eradicating the viral reservoir.