

Abstract

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TITLE: Significant Reduction of T-Cell Infectivity by CTL-targeted Con-A Delivery to HIV⁺ Reservoir APCs

ABSTRACT: (1) APCs take up infectious agents *via* CTLs. Certain agents (e.g., HIV) establish infectious endo(lyso)somal long-term reservoirs by evading intracellular degradation. We inquired whether CTL-targeted delivery of an HIV-agglutinating lectin inactivates such reservoirs. (2) Monocytes, macrophages, immature and mature dendritic cells (iDCs; mDCs) (5×10^4 – 2×10^5) were incubated (3 h; 37°C) with 0.1–10.0 μ l of DOPC/Chol/DOPE-MBP liposomes (150–200 nm) labeled with fucosylated, mannosylated (+ ctrl.), or galactosylated (– ctrl.) cholesterol (FC; MC; GC) and loaded with 50 mM calcein as a tracer dye. Also, iDCs or mDCs infected on d2–6 with M-tropic HIV-1 Ada-M or T-tropic HIV-1 Lai were treated on d1 post infection with FC liposomes loaded with 0.5 mg/ml Con-A. (3) FC and MC liposomes showed excellent CTL specificity (complete inhibition by 100 mM free L-fucose or D-mannose), time-dependent binding, and highly efficacious calcein delivery (fluorescence microscopy; flow cytometry) to all APCs. The dye most strongly accumulated endo(lyso)somally. FC liposomes showed even higher CTL affinity and uptake than MC liposomes. While iDC and mDC clustering is upregulated by HIV-1 infection, clustering of HIV⁺ DCs was normalized 8 days after treatment with ConA⁺ FC liposomes. Increased DC death rates, as observed upon HIV infection, as well as the HIV-dependent pathologic ratio between veiled and dendritiform DC morphologies were also largely normalized. HIV⁺ mDCs were coincubated with autologous HIV⁺ T cells for evaluating T-cell infection and subsequent HIV production. Compared to empty neg. ctrls., treatment with Con-A-loaded FC liposomes reduced T cell-dependent HIV synthesis (HIV p24 ELISA on d8) by 86.35% (range: 67.16%–96.70%; n = 5). (4) APC-targeted endo(lyso)somal delivery of an HIV-agglutinating lectin by FC liposomes significantly reduced *trans*-infection of T cells by HIV⁺ DCs. This approach may eliminate intracellular reservoirs of HIV-1, hepatitis C virus, and beyond.

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