To the editor:

The α4β7 integrin binds HIV envelope but does not mediate bystander killing of γδ T cells

Our previous study showed HIV envelope glycoprotein induces killing of CD4-negative Vγ2Vδ2 (referred as Vδ2) T cells by binding to CCR5 and α4β7.1 Blocking either CCR5 with receptor antagonists or α4β7 with MAdCAM1 reduced Env binding and killing of Vδ2 cells. Signaling through p38 and caspase activation were responsible for envelope-dependent cell death. However, we could not determine which of these receptors mediated death signaling. We have now investigated effects of HIV envelope on the CD4-negative Vδ1 subset of γδ T cells, which express α4β7, but not CCR5 receptor. Comparing envelope receptors and responses on Vδ1 and Vδ2, cells showed the envelope-α4β7 interaction does not generate a death signal.
V61 and V62 are 2 major types of human γδ T cells. For healthy adults, the ratio of V62:V61 cells in blood is 3:10.2 The V62:V61 cell ratios are inverted among HIV-infected individuals because V62 cells are depleted and the V61 subset is expanded.2-4 Both V61 and V62 are CD4-negative and nonpermissive for HIV infection.2 We proposed that HIV envelope–induced T-cell death might be an important mechanism for V62-cell depletion in HIV disease,1 but we do not know the effects on V61 cells that are increased during HIV disease. First, we tested for HIV-receptor expression on V61 T cells. V61 cells did not express dendritic cell–specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) or mannose receptor (data not shown), but had levels of α4β7 similar to those found on V62 cells (Figure 1A).3 CCR5, which is highly expressed on V62 cells,1 was not detected on V61 cells (Figure 1B). HIV envelope was bound to V61 cells, but at lower levels compared with V62 cells (Figure 1C). Binding was blocked completely by MAdCAM1 (Figure 1D). Next, we tested whether 3 different R5-tropic HIV envelope glycoproteins (from BaL, CN54, and CM strains) induced killing of V61 cells. We reported that BaL and CN54 glycoproteins induced cell death among V62 T cells.1 Here we show that CM-gp120 treatment killed 50% of V62 T cells based on 7-aminoactinomycin-D and annexin V staining (Figure 1E-F), but had no effect on V61 T cells (Figure 1E-F).

The α4β7 integrin binds gp120 but does not mediate HIV envelope–induced death signaling. HIV envelope did not activate p38 or caspase in V61 T cells (data not shown), showing that α4β7 does not signal the death pathway in the absence of CCR5.

In V62 cells, α4β7 may enhance killing by increasing the avidity of gp120 binding, but CCR5 is the key signaling receptor for cell death. These findings explain the differential effects of gp120 on CD4-negative V62 versus CD4-negative V61 T cells, which are mirrored in HIV patients where only V62 T cells are depleted.

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