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Unusual natural killer cell responses to HIV-1 peptides are associated with protection against maternal-infant transmission of HIV-1

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Natural killer cells play a pivotal role in innate and adaptive immunity. Innate immune defense pathways are classically distinguished by rapidity of response and "pattern" recognition of pathogens. Epitope specificity and memory are normally attributed to the adaptive compartment. In a study of HIV-specific T cell responses and maternal-infant HIV-1 transmission we have encountered robust responses among CD3-negative cells to HIV-1 peptides which we determined to be NK cells.

HIV-specific T cell and non-T cell responses among 79 HIV-1 infected women and their 76 infants were evaluated for responses to HIV-1 subtype C peptide pools (Gag, Pol, Nef, Env, and Reg [Tat, Rev, Vif, Vpu, Vpr combined] proteins) using an whole blood intracellular cytokine assay that measures IFN-gamma. Overall, 43% and 22% had CD3 neg responses to Env and Reg, respectively, and these same regions were targeted in slightly smaller proportions of their infants (15.8% and 5.3%). Minority targeting by CD3 neg cells occurred against Pol (2 HIV-1 infected mothers and one infant) and Nef (one infant). Importantly, no peptide-specific CD3 neg responses could be detected in either the 20 HIV-1 uninfected control mothers or their infants. Amino acid regions targeted by NK cells were identified on gp160, Vpu and Tat by whole genome peptide mapping of 5 HIV-1 infected women with CD3 neg responses using a whole blood ICS assay that utilizes a peptide pool and matrix design.

To establish if HIV peptide-specific CD3 neg responses may be protective in maternal-infant HIV-1 transmission, we compared 49 non-transmitting (non-TM) and 15 transmitting (TM) mothers and 44 exposed uninfected (EU) and 18 HIV-infected infants. Twenty-eight of 49 (57.1%) non-TM mothers and 13/44 (29.5%) EU infants had detectable HIV-specific CD3 neg responses. In comparison, 1/15 (6.7%) and 1/18 (5.6%) of TM mothers and infected infants, respectively had these responses ($P = 0.001$ and $P = 0.049$ for mothers and infants respectively). Adjusting for maternal viral load, the association between the presence of HIV-specific CD3 neg responses in the mothers and transmission remained statistically significant ($P = 0.01$). No other factors including maternal CD4 count, mode of delivery, infant birth weight or antiretroviral prophylactic regimens explained the association.

Therefore the presence of NK cells that respond with remarkable specificity and high magnitude to HIV-1 peptides was significantly associated with lack of maternal-infant HIV-1 transmission, suggesting a protective role of

HIV-specific NK responses within this mode of HIV-1 transmission. These findings identify an important new measure of protective immunity to HIV-1 that highlights the importance of innate immunity in preventing the establishment of HIV-1 infection.