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Oral presentation

Overcoming CD4 deficiency to induce long-lived memory CD8+ CTL

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One critical hurdle for therapeutic HIV vaccines is the deficiency of CD4+ T cell help during HIV infection. CD4+ T cell help has been shown to be necessary for induction of long-lived memory CD8+ cytotoxic T lymphocytes (CTL), and when CD8+ T cells are primed in its absence, they are susceptible to TRAIL-mediated death during secondary stimulation. We have found that IL-15 expression by a vaccine vector allowed induction of longer-lived, higher avidity memory CTL. We also observed that CD40L, a molecule by which helper T cells mediate help, induces dendritic cells to secrete IL-15. We therefore hypothesized that one mechanism by which CD4+ T helper cells induce longer-lived memory CTL may be to stimulate IL-15 production by the dendritic cell presenting antigen, and that therefore, IL-15 might overcome the need for CD4+ T cell help. We have now tested this hypothesis by demonstrating that immunization of CD4-depleted mice with a recombinant vaccinia-HIV vaccine vector expressing IL-15 induced long-lived memory CTL, whereas immunization of the depleted mice with a recombinant vaccinia-HIV vector not expressing IL-15 resulted in short-lived CTL that disappeared within two months. Further, CTL induced with the IL-15-expressing vaccine were resistant to TRAIL-mediated death on secondary stimulation, whereas those induced without IL-15 underwent apoptosis. Resistance was associated with upregulation by IL-15 of anti-apoptotic Bcl-XL and downregulation of Bax, a downstream transducer of the TRAIL death signal. These findings help explain the role of helper T cells in inducing long-lived memory CTL and provide a practical approach to overcome the deficiency of CD4+ T cell help during HIV infection for induction of CTL with a therapeutic vaccine for HIV, or with a vaccine for other opportunistic infections.