Surface-bound Tat inhibits antigen-specific CD8+ T-cell activation in an integrin-dependent manner.

The identification of still unrevealed mechanisms affecting the anti-HIV CD8 T-cell response in HIV-1 infection. Starting from the observation that anti-Tat immunization is associated with improved CD8 T-cell immunity, we developed both in-vitro and ex-vivo assays to characterize the effects of extra-cellular Tat on the adaptive CD8 T-cell response. The effects of Tat on CD8 T-cell activation were assayed using CD8 T-cell clones specific for either cellular (MART-1) or viral (HIV-1 Nef) antigens, and HIV-1 Gag-specific CD8 T cells from HIV-1 patients. The interaction between CD8 T lymphocytes and immobilized Tat, but not its soluble form, inhibits peptide-specific CD8 T-lymphocyte activation. The inhibition does not depend on Tat trans-activation activity, but on the interaction of the Tat RGD domain with \( \alpha_5 \beta_1 \) and \( \alpha_v \beta_3 \) integrins. Impaired CD8 T-cell activation was also observed in cocultures of CD8 T cells with HIV-1-infected cells. Anti-Tat Abs abrogate the inhibitory effect, consistently with the evidence that extracellular Tat accumulates on the cell membrane of virus-producing cells. The Tat-induced inhibition of cell activation associates with increased apoptosis of CD8 T cells. Finally, the inhibition of cell activation also takes place in Gag-specific CD8 T lymphocytes from HIV-1-infected patients. Our results support the idea...
that CD8 T-cell apoptosis induced by surface-bound extracellular Tat can contribute to the
dysregulation of the CD8 T-cell adaptive response against HIV as well as other pathogens present in
AIDS patients.