

Poster presentation

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PI6-47. Interleukin (IL)-21 induces cytolytic molecule perforin in CD4 and CD8 T cells without CD4 activation in chronically SIV infected rhesus macaques

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Background

IL-21 is a common g-chain utilizing cytokine derived mainly from activated CD4 T cells and T follicular helper cells with a broad range of cellular targets. We previously described perforin induction by IL-21 in human CD8 T cells with dependence on prior cellular activation and Stat-3 utilization (Blood, 2007).

Methods

To confirm its biologic activity, we conducted pilot in vivo studies of r-Mamu IL-21 in rhesus macaques.

Results

In two healthy animals a dose escalation study (1, 10, 50 and 100 microgram/kg subcutaneous IL-21 at 14 day intervals) resulted in a modest transient increase in perforin in T cells. There were no adverse events but anti-IL-21 antibody mainly to his-tag was rapidly induced. In 4 chronically SIV infected animals, IL-21 injections (2 doses, 50 microgram/kg intravenously at 7 day intervals; 3rd dose 100 microgram/kg subcutaneously 21 days after the 2nd dose) resulted in significant upregulation of perforin at all doses in CD4 and CD8 T cells in peripheral blood sampled on day 3 post dosing in comparison to 3 SIV+ control animals. Interestingly, perforin increase was noted in all CD4 and CD8 T cell subsets (naïve, central memory, effector memory) and fold increase was most prominent in naïve CD4 cells (2.7 fold, P = 0.05) and

effector memory CD8 T cells (2 fold, P = 0.0004). Perforin upregulation was accompanied by slight increase in Ki67 in CD8 T cells, but with no evidence of cellular expansion and significant decrease in HLA-DR expression in naïve and central memory CD4 T cells. No change in CD4 counts or virus load were noted. Functional virus specific T cell responses and serum anti-IL-21 determination are ongoing.

Conclusion

The novel perforin inducing property of IL-21 in CD4 and CD8 T cells without inducing CD4 T cell activation makes it an attractive molecule for consideration in immunotherapeutic and vaccine strategies.