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CD4 as a receptor for IL-16: To be or not to be?

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Keywords

CD4, CD4 knockout mice, interleukin-16

Context

IL-16 is a pro-inflammatory cytokine that induces chemoattractant, as well as proliferative, responses in $CD4^+$ T cells. It has inhibitory effects on the replication of HIV. Since the addition of OKT4 or soluble CD4 inhibits the IL-16 chemotaxis induced by IL-16, it has been suggested that IL-16 uses CD4 as its receptor. To date there is no direct proof of such an interaction between IL-16 and CD4. To investigate whether CD4 is required for the activity of IL-16, using cells derived from CD4 knockout (CD4-/-) mice.

Significant findings

After incubation with rmIL-16 for 24 h, total PBMC and monocytes from CD4+/+ mice produced increased amounts of TNF-a and IL-6, whereas total PBMCs depleted of monocytes showed no changes. No effect of rmIL-16 was found on the production of IL-1?. Control experiments with anti-IL-16 antibodies as well as soluble CD4 inhibited the IL-16-mediated responses.

Incubation of total PBMC from CD4-/- mice with rmIL-16 resulted in increased production of IL-1?, TNF-a and IL-6. Interestingly, the concentrations of TNF-a and IL-6 were generally higher than those obtained using cells from CD4+/+ mice. The addition of soluble CD4 did not inhibit the production of the three cytokines. Moreover, rmIL-16 induced chemotactic migration of PBMCs isolated from both CD4+/+ and CD4-/- mice, and the use of an anti-IL-16 antibody resulted in a significant decrease in the chemotactic response of PBMCs from both mouse strains.

Comments

There is substantial evidence that interleukin 16 (IL-16) uses CD4 as a receptor. Anti-CD4 antibodies (OKT4) and soluble CD4 inhibit IL-16-induced functions. In addition, IL-16 migratory responses, as well as rises in intracellular Ca^{2+} and inositol (1,4,5)-trisphosphate, are observed after transfection of human CD4 into L3T4-, IL-16 nonresponsive mouse T cell hybridoma cells. In this study, Mathy *et al* showed that peripheral blood mononuclear cells (PBMC) from CD4 knockout mice exhibit similar or even better responses to IL-16 than PBMC from CD4 wild-type mice. These results indicate that the presence of CD4 is not obligatory for the function of IL-16 in mouse cells. The question of whether there is another receptor for IL-16 in addition to CD4 or whether CD4 is involved only indirectly in IL-16-mediated effects needs to be addressed in further studies.

Methods

Total PBMC were isolated from CD4+/+ and CD4-/- mice (both of the C57BL/6 background). Monocytes were isolated or depleted. Isolated cells were stimulated with recombinant mouse IL-16 (rmIL-16). Levels of mouse IL-1?, IL-6 and TNF-a protein were detected by sandwich ELISA. Chemotaxis in response to rmIL-16 was assessed.

References

1. Mathy NL, Bannert N, Norley SG, Kurth R: CD4 is not required for the functional activity of IL-16. J Immunol. 2000, 164: 4429-4432.