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# Anti-CD3-activated killer T cells: Interleukin-6 modulates the induction of major histocompatibility complex-unrestricted cytotoxicity and the expression of genes coding for cytotoxic effector molecules.

Greene AL, **Makrigiannis** AP, Fitzpatrick L, Hoskin DW.

Department of Microbiology and Immunology, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.

## Abstract

We have investigated the role of interleukin-6 (IL-6) in the induction of major histocompatibility complex (MHC)-unrestricted cytotoxicity, as well as granzyme B, perforin, and Fas ligand gene expression, following mouse T lymphocyte activation with anti-CD3 monoclonal antibody (mAb). The generation of anti-CD3-activated killer-T (AK-T) cells was inhibited when anti-IL-6 neutralizing mAb was added at initiation of culture but not 24 h later, indicating that IL-6 is involved at an early stage of AK-T cell development. However, AK-T cell induction in the presence of exogenous IL-6 did not result in enhanced cytotoxicity, suggesting that saturating levels of IL-6 are normally synthesized in AK-T cell cultures. The inhibitory effect of IL-6 neutralization on AK-T cell generation could not be attributed to a defect in AK-T cell proliferation or to an inability of AK-T cells to recognize and adhere to P815 tumor target cells. However, IL-2 synthesis and CD25 expression were downregulated in AK-T cell cultures performed in the presence of anti-IL-6 mAb. In addition, IL-6 neutralization resulted in decreased expression of granzyme B and perforin, but not Fas ligand, mRNA. Exogenous IL-2 (50 U/ml) added at initiation of culture completely reversed the inhibitory effect of anti-IL-6 mAb on AK-T cell development, restoring CD25 expression and tumoricidal activity, as well as granzyme B and perforin mRNA expression, to control levels. We conclude that IL-6 modulates AK-T cell induction through an IL-2-dependent mechanism.

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