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Growth regulation of simian and human AIDS-related non-Hodgkin's lymphoma cell lines by TGF- β 1 and IL-6

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Abstract

Background: AIDS-related non-Hodgkin's lymphoma (AIDS-NHL) is the second most frequent cancer associated with AIDS, and is a frequent cause of death in HIV-infected individuals. Experimental analysis of AIDS-NHL has been facilitated by the availability of an excellent animal model, i.e., simian Acquired Immunodeficiency Syndrome (SAIDS) in the rhesus macaque consequent to infection with simian immunodeficiency virus. A recent study of SAIDS-NHL demonstrated a lymphoma-derived cell line to be sensitive to the growth inhibitory effects of the ubiquitous cytokine, transforming growth factor-beta (TGF-beta). The authors concluded that TGF-beta acts as a negative growth regulator of the lymphoma-derived cell line and, potentially, as an inhibitory factor in the regulatory network of AIDS-related lymphomagenesis. The present study was conducted to assess whether other SAIDS-NHL and AIDS-NHL cell lines are similarly sensitive to the growth inhibitory effects of TGF-beta, and to test the hypothesis that interleukin-6 (IL-6) may represent a counteracting positive influence in their growth regulation.

Methods: Growth stimulation or inhibition in response to cytokine treatment was quantified using trypan blue exclusion or colorimetric MTT assay. Intracellular flow cytometry was used to analyze the activation of signaling pathways and to examine the expression of anti-apoptotic proteins and distinguishing hallmarks of AIDS-NHL subclass. Apoptosis was quantified by flow cytometric analysis of cell populations with sub-G1 DNA content and by measuring activated caspase-3.

Results: Results confirmed the sensitivity of LCL8664, an immunoblastic SAIDS-NHL cell line, to TGF-beta1-mediated growth inhibition, and further demonstrated the partial rescue by simultaneous treatment with IL-6. IL-6 was shown to activate STAT3, even in the presence of TGF-beta1, and thereby to activate proliferative and anti-apoptotic pathways. By comparison, human AIDS-NHL cell lines differed in their responsiveness to TGF-beta1 and IL-6. Analysis of a recently derived AIDS-NHL cell line, UMCL01-101, indicated that it represents immunoblastic AIDS-DLBCL. Like LCL-8664, UMCL01-101 was sensitive to TGF-beta1-mediated inhibition, rescued partially by IL-6, and demonstrated rapid STAT3 activation following IL-6 treatment even in the presence of TGF-beta1.

Conclusion: These studies indicate that the sensitivity of immunoblastic AIDS- or SAIDS-DLBCL to TGF-beta1-mediated growth inhibition may be overcome through the stimulation of proliferative and anti-apoptotic signals by IL-6, particularly through the rapid activation of STAT3.