RAPID COMMUNICATION

Interleukin-10 Is an Autocrine Growth Factor for Acquired Immunodeficiency Syndrome-Related B-Cell Lymphoma

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Interleukin-10 (IL-10) is an acid-sensitive protein of 35 kD that has pleiotropic effects including inhibition of cytotoxic T-cell response, induction of major histocompatibility complex type II in B lymphocytes, induction of B-cell growth and differentiation, and autocrine growth factor activity in monocytes. We and others have shown that IL-10 is produced spontaneously by blood mononuclear cells from human immunodeficiency virus-seropositive patients. In an attempt to ascertain the potential role of IL-10 in acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma, we evaluated the expression of human IL-10 in both tumor-derived B-cell lines and primary tumor cells. Expression of human IL-10 (hIL-10) mRNA and protein was detected in four of five cell lines examined. An hIL-10 antisense oligonucleotide inhibited hIL-10 mRNA expression and hIL-10 protein production. The proliferation of all B-cell lines was inhibited by an antisense oligonucleotide in a dose-dependent manner that was abrogated by the addition of recombinant hIL-10 protein. No effect of antisense oligonucleotide was observed in the B-cell line not producing hIL-10. Evaluation of primary tumor cells from patients with AIDS-related lymphoma cells showed similar production and response to IL-10. These data suggest an autocrine growth mechanism for IL-10 in AIDS-related lymphoma cells and that IL-10 may be important in its pathogenesis.

MALIGNANT B-cell lymphoma occurs with increased frequency in a number of conditions associated with immune dysregulation. The most dramatic example of this relationship is the development of high-grade B-cell lymphoma in patients with human immunodeficiency virus-1 (HIV-1) infection. The risk of development of B-cell lymphoma increases rapidly over time in these patients with underlying poor immune function, characterized by low CD4+ lymphocyte counts in the peripheral blood. Furthermore, reactivation of Epstein-Barr Virus (EBV) and expansion of EBV-positive B-cell clones in the lymphoid tissue may precede the development of lymphoma as suggested by the presence of EBV DNA in 40% to 65% of systemic acquired immunodeficiency syndrome (AIDS) lymphomas. In addition, HIV-seropositive patients frequently exhibit spontaneous B-cell activation with increased Ig production. Thus, the pathogenesis of AIDS-related lymphoma has been hypothesized to involve the induction of B-cell proliferation through one or multiple signals followed by transforming genetic events.

Multiple growth regulatory proteins (cytokines) have been postulated to contribute to the development of hematologic malignancies. Specifically, interleukin-4 (IL-4) and IL-6 have been shown to affect the proliferation and differentiation of B lymphocytes; thus, these two cytokines may function as autocrine growth factors in B-cell lymphoma. IL-10 has multiple effects on B lymphocytes, including stimulation of growth and differentiation, and thus may contribute to the development of B-cell lymphoma. For example, sequence analysis of IL-10 shows homology to a previously uncharacterized open reading frame in the EBV genome, designated BCRF-1. The BCRF-1 gene product (viral IL-10) can induce cellular IL-10 and can substitute in function for many biologic activities of human IL-10 (hIL-10). In addition, B lymphocytes produce and also respond to IL-10; hence, this cytokine might act as an autocrine growth factor in human lymphoid tumors. Increased serum levels of IL-10 have been reported in patients with lymphoma, both with and without underlying HIV-1 infection, and such increases have been associated with poor survival. The role of IL-10 in the development of AIDS-related lymphoma is currently unknown. The present study was performed to determine the role of IL-10 in the proliferation of AIDS-related B-cell lymphomas through in vitro analysis of both primary tumor cells and tumor-derived cell lines.

MATERIALS AND METHODS

Reagents. Recombinant hIL-10 cDNA was kindly provided by Kevin Moore (DNAX, Palo Alto, CA). Formalinized particles of Staphylococcus aureus strain Cowan I (SAC) were purchased as Pansorbin from Cal Biochem-Behring (La Jolla, CA). Mouse monoclonal antibodies (MoAbs) to human CD3, CD4, and CD14 were purchased from Sigma Chemical Co (St Louis, MO). Fluorescein isothiocyanate (FITC)-conjugated F(ab')2 of sheep antimouse antibody was purchased from Ortho Pharmaceutical Diagnostic Systems (Raritan, NJ). Bio-Magnetic Goat Anti-Mouse IgG was purchased from Advanced Magnetics, Inc (Cambridge, MA).

Cells and cell lines. Primary tumor tissue from five patients with HIV-related non-Hodgkin's lymphoma were freshly obtained and analyzed.

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immortal B-cell lines were established. All five cell lines (23-1 to 23-5) were of B-cell lineage as shown by Ig heavy chain rearrangement. Evidence for EBV genome was present in four of five cell lines. The cell lines were maintained in RPMI 1640 and 10% fetal calf serum (FCS; heat-inactivated). In addition, the following controls were used: T-cell (HUT-78), promonocytic (U-937), fibroblast (T1), myeloma (U-266), and promyelocytic (HL-60) cell lines. These controls were each maintained in RPMI 1640 supplemented with 10% FCS (heat-inactivated), 100 µg/mL streptomycin, and 100 U/mL penicillin.

Northern blot. Total RNA was extracted by guanidinium thiocyanate29 (RNAzol; Tel-Test, Inc, Friendwood, TX) and 15 µg of total RNA was analyzed by electrophoresis through 1% agarose formaldehyde gels followed by transfer to nylon membranes. RNA blots were prehybridized at 68°C for at least 30 minutes in QuikHyb

(Stratagene, San Diego, CA) containing 100 µg salmon sperm DNA (Stratagene). The plasmid DNA encoding human IL-10 was restriction enzyme digested with Bgl II and HindIII to generate a 760-bp fragment that was gel purified and used as a probe. The DNA was radiolabeled using the Random Primer Labeling Kit (Boehringer Mannheim, Indianapolis, IN) with [α-32P]dCTP (3,000 Ci/mmol; DuPont, Boston, MA). The membrane was hybridized for 4 hours and the filter was washed twice in 2× SSC and 0.1% sodium dodecyl sulfate (SDS) at room temperature for 15 minutes each and once in 0.1× SSC and 0.1% SDS at 60°C for 30 minutes. Membranes were placed at −70°C and exposed to Hyperfilm-MP (Amersham, Arlington Heights, IL). The probe was stripped in 50% formamide in 1× SSPE at 70°C for 2 hours and the membranes were reprobed with 32P-radiolabeled β-actin cDNA to confirm the integrity and relative amounts of RNA in each lane.

![Figure 1](image-url)
Amplification of IL-10 mRNA using reverse transcriptase-polymerase chain reaction (RT-PCR). We used the RT-PCR technique to detect the expression of hIL-10 in B-cell lines. cDNA was prepared by reverse transcription of ~2.0 µg total RNA using oligo dT as a primer in a total volume of 20 µL (Superscript; Gibco BRL, Gaithersburg, MD). Five microliters of cDNA solution was amplified with 2.5 U of Taq Polymerase (Perkin Elmer) and 50 pmol of each of the 5’ and 3’ primers, dNTP (2.5 mmol/L), and MgCl2 (1.5 mmol/L) in a total volume of 50 µL. The samples were amplified for 35 cycles. Each cycle consisted of denaturing at 94°C for 60 seconds, primer annealing at 60°C for 60 seconds, and extending at 72°C for 2 minutes. To ensure that specific amplification of hIL-10 was achieved, we used two primers that do not generate an amplified fragment from plasmid templates containing the BCRF1 open reading frame from EBV that is homologous to hIL-10. Primer 1 was composed of the protein coding nucleotides 323 to 349 (sense strand) 5’ CTG-ACA-ACC-AAG-ACC-CAG-ACA-TCA-AGG; primer 2 corresponded to nucleotides 648-674 from the 3’ untranslated region (antisense strand) 5’ CAA-TAA-GGT-TTC-TCA-AGG-GGC-TGG-GTC. A positive reaction yielded a 350-bp amplification product that was visualized on an ethidium bromide-stained 1.5% agarose gel and confirmed with hybridization to 32P-radiolabeled internal oligodeoxynucleotide probe composed of nucleotides 381 to 422. Control PCR reactions using RNA uniformly failed to generate any product, confirming the absence of genomic DNA contamination (data not shown). As a control, all samples analyzed for hIL-10 expression by RT-PCR were also tested for expression of β-actin. Nucleotide sequences for oligonucleotide 5’ primer (sense strand) and 3’ primer (antisense strand) for β-actin were GTGGGCGGC-CACCAGCCACCA and CTCCCTAAATGTCCAGCGATTTC, respectively. Samples were amplified for 30 cycles. The amplified product of 548 bp was visualized in a 1.0% agarose gel containing ethidium bromide.

Measurement of IL-10. IL-10 was assayed using two MoAbs specific for two separate epitopes on IL-10. MoAb (9D7) was first coated onto the wells of 96-well round-bottom plates. The supernatants from various cell lines, including standards of known recombinant IL-10 content, were added to the wells followed by the addition of a haptenated (nitroiodophenyl) secondary antibody (12G8). During the first incubation, the IL-10 antibody bound simultaneously to both immobilized (capture) antibody on one site and to the solution phase haptenated antibody on a second site. After removal of excess secondary antibody, horseradish peroxidase (HRP)-conjugated anti-NIP(J4) was added that bound to the haptenated antibody to complete the four-member sandwich. After a second incubation and wash, substrate solution [2,2’-azino-bis (2-ethyl benzthiazoline-6-sulfonic acid; Sigma] was added, and absorption was measured using an enzyme-linked immunosorbent assay (ELISA) reader at 490 nm wavelength. Assays using these antibodies measure both viral and human IL-10, whereas antibodies (JESS-2B102 and JES3-26H4) measured human but not viral IL-10.

IL-10 sense and antisense oligonucleotides. A 20-base phosphothioate-modified sense oligonucleotide (5’ ATGCAAGGCTCA-GCACTGCT) corresponding to nucleotides +31 to +50 of the hIL-10 coding regions and the complementary antisense oligonucleotide (5’ AGCAAGGTGATCGTGTGCAT) were synthesized and purified by Operon Technologies, Inc (Alameda, CA). Established B-cell lines were suspended in RPMI 1640 medium containing 10% FCS, and 200 μL of cells (5 x 10⁶ cells/well) was added to each well of the 96-well plate treated with various concentrations of both oligonucleotides (0 to 10 μmol/L), with or without recombinant IL-10 (10 ng/mL), at 37°C for 3 days. The supernatants were collected and stored at −70°C until testing for IL-10 protein by ELISA. Cell proliferation was measured by [3H] thymidine incorporation. Two other pairs of sense and antisense oligonucleotides corresponding to region −27 to −13 and to region +1 to +15 were also synthesized and tested as described above. These latter antisense oligonucleotide failed to effectively inhibit IL-10 expression and thus were not used in subsequent experiments. Established B-cell lines were also treated twice every 24 hours with various concentrations of IL-10 sense and antisense oligonucleotides. Total RNA was isolated and cDNA was synthesized and IL-10 and β-actin activity were measured by PCR.

Isolation and purification of B-lymphoma cells. Heparinized peripheral blood was obtained from healthy donors. Fresh lymphoma tissues or malignant ascites were obtained from patients with AIDS-related high-grade B-cell lymphoma. Tissue was minced and passed through a cell strainer (Falcon, catalogue no. 2350) to prepare a single-cell suspension in RPMI 1640 medium containing 10% FCS, 2 mmol/L L-glutamine, penicillin, streptomycin, and 10% FCS (heat-inactivated). Flow cytometric analysis showed greater than 95% CD19 reactivity. Peripheral blood mononuclear cells (PBMCs) and primary lymphoma cells were incubated at 4°C for 30 minutes. After washing twice with phosphate-buffered saline (PBS), antibody-bound cells were removed using magnetic beads (Advanced Magnetics, Inc) coated with antitumor IgG. Unbound cells were washed twice with Hank’s Buffered Saline Solution (HBSS) and resuspended (10⁶ cells/mL) in RPMI 1640 with 2 mmol/L L-glutamine, penicillin, streptomycin, and 5% FCS (heat-inactivated). Flow cytometric analysis showed greater than 95% CD19 reactivity of the resultant cell population. Purified B-cell populations were cultured for 24 hours and the supernatant IL-10 levels were measured by ELISA.

Thymidine incorporation assay. Purified B cells from healthy donors and lymphoma tissues were resuspended (10⁶ cells/mL) in RPMI 1640 with 2 mmol/L L-glutamine, penicillin, streptomycin, and 5% FCS (heat-inactivated) and 200 µL of cells (2 x 10⁶ cells/well) were preactivated for 48 hours with various concentrations of SAC (0, 0.05, and 0.5 μL/mL) in 96-well plates. Preactivated cells were further treated with IL-10 (5 and 25 ng/mL) at 37°C for another 2 days. In three cases, cells isolated from patients were treated with IL-10 Ab (1 μg/mL) alone or with recombinant IL-10 (10 ng/mL). For proliferation assays, cells were incubated with 1 μCi of [3H] thymidine for 16 hours on day 4. The cells were then harvested onto glass filters using a Packard Harvester (Meriden, CT) and [3H] thymidine incorporation was quantitated by liquid scintillation counting. The assays were performed in triplicate.

RESULTS

IL-10 mRNA expression and protein production by HIV-related B-cell lymphoma. Five AIDS-related lymphoma B-cell lines were analyzed for the presence of IL-10 mRNA using RT-PCR. All of the cell lines tested positive for IL-10 mRNA. The detection limit was 0.004 ng.
Fig 2. Effect of an IL-10 antisense oligonucleotide on cell growth of AIDS-lymphoma B-cell lines. B-cell lines (A) 23-2, (B) 23-4, and (C) 23-1 were incubated with IL-10 (■) sense or (Ⅲ) an antisense oligonucleotide at concentrations from 1 to 10 μmol/L. Cells were harvested on day 3; cell proliferation was measured by [3H] thymidine incorporation after 16 hours. (D) Inhibition of cell growth in AIDS-lymphoma B-cell line 23-2 by IL-10 antisense was blocked by addition of recombinant human IL-10. Cells were incubated with various concentrations of IL-10 sense (S) or antisense (AS) oligonucleotides with and without recombinant hIL-10 (10 ng/mL). (■) rIL-10 + IL-10 sense; (●) rIL-10 + IL-10 antisense; (□) IL-10 sense; (Ⅲ) IL-10 antisense. Cell proliferation was measured after 3 days. Data represent the mean ± standard deviation of three experiments performed in quadruplicate.

The supernatants from cell lines were then tested for secretion of hIL-10 protein by ELISA (Table 1). hIL-10 protein was detected in only the 4 cell lines expressing hIL-10 mRNA by RT-PCR. As expected, the cell lines expressing the highest levels of hIL-10 mRNA secreted more hIL-10. The T-cell control, HUT-78, which was derived from a patient with cutaneous T-cell lymphoma (HUT-78), also expressed high levels of IL-10 (Table 1).

IL-10 is an autocrine growth factor for B-cell lymphoma. An antisense oligonucleotide corresponding to three different regions (−27 to −13, +1 to +15, and +31 to +50) of IL-10 mRNA was tested for activity against B-cell lymphoma lines. Only one of the three antisense oligonucleotides tested showed inhibitory activity, whereas all sense oligonucleotides were inactive. All subsequent experiments were thus performed with oligonucleotides corresponding to nucleotides +31 to +50 of hIL-10 coding regions.
IL-10: GROWTH FACTOR FOR B-CELL LYMPHOMA

To determine whether hIL-10 functions as an autocrine growth factor in AIDS-related lymphoma cells, hIL-10--specific oligonucleotides (sense and antisense) were tested at various concentrations in a cell proliferation assay. An antisense oligonucleotide specific for hIL-10 inhibited the growth of all hIL-10--producing cell lines (23-2 and 23-4), regardless of EBV status. These data provide evidence that cellular hIL-10 but not viral IL-10 modulates cell growth (Fig 2A and B). The specificity of this effect was supported by lack of effect of control oligonucleotides on these cell lines and by the absence of growth inhibition by an antisense oligonucleotide on the cell line 23-1, which does not express IL-10 (Fig 2C). The maximum inhibitory effect on IL-10 expressing cell lines was noted at oligonucleotide concentrations of 5 to 10 μmol/L, which inhibited cell proliferation by more than 60%.

We also showed the specificity of the hIL-10 antisense oligonucleotide by the ability of rhIL-10 to rescue cells previously treated with an antisense oligonucleotide. Antisense alone inhibited the growth of B-lymphoma cell lines that expressed IL-10. Addition of rhIL-10 to the cells treated with an antisense oligonucleotide completely abrogated the antisense inhibitory effects (Fig 2D). These data confirmed that the inhibitory effect of the oligonucleotide was not caused by a nonspecific expression of cellular proliferation.

An antisense oligonucleotide inhibits IL-10 production. IL-10 mRNA was completely depleted by an antisense treatment, whereas cells treated with the complementary sense oligonucleotide had IL-10 mRNA levels equivalent to controls. hIL-10 mRNA was measured by semiquantitative methods with various concentrations of IL-10 antisense and sense oligonucleotides by RT-PCR. Treatment with 1 μmol/L and greater levels of IL-10 antisense oligonucleotide for 48 hours resulted in a decrease in IL-10 mRNA compared with that in untreated controls. No IL-10 mRNA was detected in cells treated with IL-10 antisense oligonucleotide at concentrations of 2.5 μmol/L and greater (Fig 3A). In contrast, cells treated with various concentrations of IL-10 sense oligonucleotide (1 to 10 μmol/L) did not show a decrease in IL-10 mRNA. Integrity of mRNA was confirmed by the amplification of β-actin in all samples (Fig 3A).

Fig 3. Effect of an IL-10 antisense oligonucleotide on IL-10 expression. (A) hIL-10 mRNA levels detected by RT-PCR. mRNA was isolated from B-cell lymphoma line 23-2 treated with various concentrations of IL-10 (sense and antisense oligonucleotides). RT-PCR was used to detect IL-10 and β-actin. The supernatant of B-cell lines (B) 23-2 and (C) 23-4 were collected after IL-10 sense/antisense treatment and assayed for IL-10 by ELISA. The data represent the mean ± standard deviation of three experiments performed in quadruplicate.

Fig 4. IL-10 levels were determined by ELISA in supernatant of primary B-lymphoma cells obtained from HIV-positive (197) and HIV-negative (198) patients. Primary cell cultures were incubated with various concentrations of SAC and supernatant was collected after 48 hours for the measurement of IL-10 levels by ELISA.
Supernatant from antisense-treated lymphoma cells was also analyzed for IL-10 protein levels by ELISA. We observed a dose-dependent suppression of hIL-10 production in cell lines (23-2 and 23-4) treated with an antisense oligonucleotide. Sense oligonucleotides had no significant inhibition at concentrations up to 5 μmol/L. Higher concentrations had nonspecific toxicity (Fig 3B and C). We have thus shown by three different methods that IL-10 antisense oligonucleotide specifically blocks the production of IL-10 protein and its function.
IL-10 is produced by primary B-lymphoma cells. Unstimulated B cells from healthy donors do not produce detectable levels of IL-10. In contrast, primary AIDS-related lymphoma cells secrete substantial amounts of IL-10, which was further enhanced by mitogenic stimulation with SAC (Fig 4). Whereas primary B-lymphoma cell preparations may have contaminating monocyte/macrophages or T cells that may contribute to IL-10 production, the induction by SAC is highly suggestive of a B-cell source of this protein.

IL-10 is a comitogen for B-cell lymphoma. Healthy donor B lymphocytes proliferate in response to IL-10 when costimulated with B-cell mitogens such as SAC. To determine the response to IL-10, we studied primary B-lymphoma cells from 8 patients: 4 HIV-seropositive and 4 HIV-seronegative patients (Fig 5). IL-10 alone at concentrations of 5 and 25 ng/mL had no significant effects. However, IL-10 significantly enhanced DNA synthesis when primary lymphoma B cells were first exposed to SAC, regardless of the HIV status.

Antagonism of IL-10 inhibits primary B-lymphoma cell proliferation. Unstimulated primary B-lymphoma cells rarely show substantial DNA synthesis and cell proliferative potential when tested in the presence or absence of IL-10. In three cases examined, all showed inhibition of DNA synthesis when treated with neutralizing antibody to IL-10 under unstimulated or SAC-stimulated conditions (Fig 6). These data suggest that primary AIDS-lymphoma cells both produce IL-10 and use it for their growth.

Exogenous rhIL-10 also acted as a comitogen on primary B-lymphoma cells stimulated with SAC. The effect was dose dependent and similar to the IL-10 effect on healthy donor B cells. The addition of neutralizing IL-10 antibody (JES3) completely abrogated the stimulatory effect of SAC and IL-10. Thus, IL-10 is also a paracrine growth factor for primary B-lymphoma cells.

DISCUSSION

IL-10 is known to induce proliferation and differentiation of normal B lymphocytes and increased IL-10 levels have been observed in nearly 50% of patients with malignant lymphomas and may be predictive of poor survival. Of interest, HIV-1 infection is also associated with increased IL-10 levels both in the presence and absence of concurrent malignant lymphoma. In HIV-1-seropositive patients, IL-10 is produced spontaneously by PBMCs, including monocytes and T cells. Furthermore, IL-10 levels increase with worsening immune function and decreasing levels of CD4 lymphocytes. This corresponds to the period in HIV-1 infection when the risk for development of lymphoma increases.

In this report, we document that B-lymphoma cell lines developed from patients with AIDS-related lymphoma produce large amounts of IL-10, similar to that previously reported by others. Furthermore, our data indicate that IL-10 production correlates with latent EBV infection similar to that reported by Emilie et al, in which IL-10 expression was documented in 50% of tumor tissue from patients with AIDS-related lymphoma.

We evaluated whether IL-10 expression was associated with autocrine stimulation of AIDS-related lymphoma cells. We studied this through the inhibition of IL-10 expression using a specific antisense oligonucleotide and by assessing the effect of neutralizing antibodies. We showed that an antisense oligonucleotide corresponding to nucleotides +31 to +50 of hIL-10 coding region effectively inhibited IL-10 mRNA expression and protein production, whereas the sense oligonucleotide to the same region had marginal effect. This effect was correlated with a dose-dependent inhibition of cellular proliferation as measured by 3H-thymidine incorporation. Inhibition by antisense oligonucleotide was significantly different from the nonspecific inhibitory effects of sense oligonucleotides seen at higher concentrations. Furthermore, addition of rhIL-10 to the antisense-treated cultures completely overcame the suppression of cell growth.

We then assessed whether these phenomena also occurred in primary tumor tissue. B-lymphoma cells isolated from patients with AIDS-lymphoma proliferated in response to IL-10, particularly in the setting of SAC activation.
primary AIDS-lymphoma cells produced IL-10 spontaneously, and neutralizing IL-10 antibody inhibited the proliferation of resting or stimulated cells.

Coupled with our previous data that HIV is capable of inducing IL-10 production, it is possible that IL-10 may have a central role in the pathogenesis of AIDS lymphoma. Our findings support the possibility that inhibiting IL-10 may have a therapeutic potential in the treatment of patients with AIDS-related lymphomas.

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