Human Interleukin-3 mRNA Accumulation Is Controlled at Both the Transcriptional and Posttranscriptional Level


Interleukin-3 (IL-3) is a hematopoietic growth factor that regulates the differentiation of multilineage and committed progenitor cells and the functions of some mature blood cells. The expression of human IL-3 appears to be restricted to stimulated T lymphocytes. We have investigated the kinetics and mechanisms involved in the induction of IL-3 expression in the human T lymphocytic tumor cell line Jurkat. We show that accumulation of IL-3 mRNA is controlled at both the transcriptional and posttranscriptional level. Transcription of the IL-3 gene in these cells appears to be constitutive but no IL-3 mRNA was detected in unstimulated cells, indicating that in resting cells IL-3 mRNA is highly unstable. Treatment with phytohemagglutinin (PHA) induced a small and transient increase in the IL-3 gene transcription rate and led to the production of detectable levels of IL-3 mRNA and protein. Optimal induction of IL-3 expression required a second stimulus. Costimulation of Jurkat cells with both phorbol myristate acetate and PHA caused both a transient increase in IL-3 gene transcription, which is dependent on new protein synthesis, and also a transient increase in mRNA stability.

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HUMAN INTERLEUKIN-3 (IL-3) is a hematopoietic growth factor (HGF) that regulates the production and functional activity of blood cells. IL-3 supports the proliferation and differentiation of a range of hematopoietic progenitor cells in vitro giving rise to granulocytic, monocytic, erythroid, mast cell, megakaryocytic, and mixed colonies. In addition, human IL-3 stimulates mature basophils, eosinophils, and monocytes to become functionally activated and so may play a role in situations of inflammation. IL-3 is distinct among the HGFs in having the capacity to stimulate progenitor cell renewal.

In contrast to other HGFs, expression of the human IL-3 gene has been demonstrated only in T-lymphocyte–enriched fractions of blood mononuclear cells and purified CD28+ T lymphocytes, as well as certain T-lymphocyte cell lines. Expression of IL-3 is induced in these cells by various stimuli including treatment with anti-T11 antibodies; either IL-1, IL-2, or anti-CD28 antibody together with stimulation of the T-cell receptor/CD3 complex with anti-CD3 or with phytohemagglutinin (PHA) in combination with phorbol myristate acetate (PMA) (PHA/PMA). The expression of other cytokines including IL-2, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon (INFγ) is also inducible in human T lymphocytes by similar stimuli. For these HGF genes both transcriptional and posttranscriptional mechanisms have been proposed in the control of mRNA levels in various cell types.

Several features of the HGF genes may be relevant to control of both transcription and mRNA stability. Although the coding regions of these genes show very little sequence homology, both the 5’ and 3’ flanking sequences of human and murine IL-3, GM-CSF, and several other HGF genes show some degree of conservation. The functions of some of the common 5’ flanking promoter sequences have been determined for the GM-CSF gene. Nuclear factors that bind to these putative regulatory elements have also been identified.

A feature common to IL-3 and several HGF mRNAs is an AU-rich sequence in the 3’ untranslated region that mediates selective mRNA degradation. Similar sequences are also found in several other transiently expressed lymphokines. These AU-rich sequences have also been implicated in the modulation of translational efficiency in vitro and in Xenopus oocytes.

We have examined the kinetics of IL-3 mRNA accumulation in the human T-cell line Jurkat. In contrast to other HGF genes, IL-3 appears to be constitutively transcribed in these cells, but there is no detectable mRNA. Treatment with PHA alone produced a small transient increase in the IL-3 gene transcription rate and led to detectable levels of IL-3 mRNA and protein. PMA together with PHA further increased the IL-3 gene transcription rate and caused an alteration of IL-3 mRNA stability, leading to greater accumulation of IL-3 mRNA and protein. We also show that while the accumulation of IL-3 mRNA can occur in stimulated cells in the absence of protein synthesis, increased IL-3 gene transcription is dependent on new protein synthesis.

MATERIALS AND METHODS

Culture and stimulation of T-lymphocyte lines. The T-lymphocyte line Jurkat was maintained in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, 1 mmol/L L-glutamine, penicillin (100 U/mL) and streptomycin (100 μg/mL). Cells were stimulated with calcium ionophore A23187 (Boehringer, Mannheim, Germany) (10^-6 mol/L), phorbol 12-myristate 13-acetate (PMA; Sigma, St Louis, MO) (20 ng/mL), and PHA (Wellcome, Dartford, England) (2 μg/mL) for the times indicated in individual experiments. Cycloheximide (CHX; Boehringer) was used at 10 μg/mL and actinomycin D (Boehringer) at 10 μg/mL, a level sufficient to inhibit 3H-uridine incorporation by 90% within 5 minutes.

RNA isolation and ribonuclease protection analysis. Cells were lysed in guanidium thiocyanate and total RNA was extracted as described. Transcription templates for high specific activity 32P-labeled RNA probes were prepared by cloning both the 301-bp Sma I/Pst I fragment of the genomic IL-3 clone J1.62 gift from

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S.C. Clark, Genetics Institute, Cambridge, MA) and the 130-bp Pst I/Sma I fragment of the β-actin cDNA from plasmid pHF A-1 into pSP64.23 Transcription reactions using SP6 RNA polymerase (Bresatec, Adelaide, Australia) were performed as described.23 Hybridization reactions included approximately 5 × 106 cpm each of the IL-3 and β-actin RNA probes and 10 or 20 μg of sample RNA. Conditions for hybridization and RNAse digestion were as described.23 Undigested RNA fragments were electrophoresed on 6% acrylamide gels containing 5 mol/L urea and autoradiographed. Quantitation of mRNA levels was by densitometry using a Gel Scan XL laser densitometer (Pharmacia LKB, Uppsala, Sweden) or by liquid scintillation counting of bands excised from the gel using a Packard (Downers Grove, IL) 2000CA liquid scintillation counter.

Transcription in isolated nuclei. Cells were harvested, washed once in cold phosphate-buffered saline (PBS), and nuclei prepared by placing the cells in lysis buffer (3 mmol/L MgCl2, 10 mmol/L Tris pH 7.4, 1 mmol/L KCl) containing 0.1% NP40 and pelleting through a cushion of 1.5 mol/L sucrose in lysis buffer without detergent at 1,500g for 5 minutes. Nuclei were then resuspended in nuclear storage buffer (40% glycerol, 5 mmol/L Tris pH 7.4, 5 mmol/L MgCl2, 0.1 mmol/L EDTA) at approximately 2.5 × 106/mL and frozen in 210-μL aliquots in liquid nitrogen until needed. Transcription reactions were performed as described24 and typically generated about 1 to 3 × 106 cpm of 32P-labeled RNA. The hybridization target plasmids were pSP64 containing the following inserts: a 10-kb genomic HindIII fragment of the IL-3 gene, a 865-bp Xho I fragment of gibbon IL-3 cDNA,25 a 5.2-kb genomic GM-CSF fragment from plasmid pCH5.2 (gift from J. Gasson, University of California at Los Angeles),26 a 1.8-kb c-fos cDNA fragment from pBK28 (gift from I. Verma, Salk Institute, La Jolla, CA) and the 2.1-kb β-actin fragment of plasmid pHF-AI.27 pSP64 plasmid DNA was used as a negative control. Target plasmids were denatured by adding NaOH to a final concentration of 0.2 mol/L and incubating at 37°C for 30 minutes. Nine volumes of 2 mol/L ammonium acetate were then added and the DNA solution was applied to nylon filters (Hybond N, Amersham, Arlington Heights, IL) using a dot-blot apparatus (Biorad, Richmond, CA). Equivalent amounts of radioactivity from the transcription reactions were hybridized to the filters in 3 mL hybridization solution (50% formamide, 25 mmol/L sodium pyrophosphate, 100 μg/mL denatured salmon sperm DNA, 1X Denhardt’s solution,27 and 0.5% sodium dodecyl sulphate (SDS) at 45°C for at least 48 hours. The filters were washed once in 2X SSC,27 0.1% SDS for 30 minutes at room temperature, and in 0.1X SSC, 0.1% SDS at 45°C for 20 minutes followed by RNAse A digestion (5 μg/mL) in 2X SSC at 37°C for 15 minutes. Filters were autoradiographed at -70°C with intensifying screens. Transcriptional rates were quantified by densitometry or by liquid scintillation counting of filter-bound RNA. Fold increases in IL-3 transcription were calculated by normalising results with respect to the β-actin signal.

Measurement of IL-3 protein. Human IL-3 protein was quantified by means of a competitive radioimmunoassay (RIA) using
REGULATION OF IL-3 GENE EXPRESSION

Fig 2. Production of IL-3 protein by stimulated Jurkat cells. Jurkat cells were grown to an initial density of 5 x 10^6/mL. One-milliliter supernatant aliquots were collected from unstimulated cells (- - -), cells pretreated with CHX for 1 hour before PMA/PHA stimulation (---), PHA (2 nM/mL)-stimulated cells (---), or PHA/PMA (2 nM/mL)/ (20 nM/mL)-stimulated cells (---) at various times after stimulation. The level of IL-3 in these aliquots was measured by RIA. Results (ng/mL) are presented as mean (2 SE) of three experiments with triplicates in each experiment.

^125^I-IL-3 and rabbit anti-IL-3 serum. A modified IL-3 protein with an added octapeptide in the amino-terminus containing an extra tyrosine to facilitate iodination (gift from L.S. Park, Immunex, Seattle, WA) was radiiodinated using the iodine monochloride method as previously described. This IL-3 has been shown to have the same properties as the unmodified IL-3. The rabbit anti-IL-3 serum (gift from S.C. Clark, Genetics Institute) was found in preliminary experiments to recognize IL-3 but not GM-CSF. Rabbit anti-IL-3 antiserum at a dilution of 1:20,000 was mixed and incubated overnight at 4°C with tissue culture supernatants or with known concentrations of CHO-derived, unlabeled IL-3 (gift from S.C. Clark, Genetics Institute, Cambridge, MA) to construct a standard curve. Fifty picomoles of ^125^I-IL-3 was then added to the mixture for a further 4 hours at 4°C. At the end of this incubation period 200 µL of previously titrated goat anti-rabbit IgG coupled to polyacrylamide beads (Biorad) was added, the mixtures centrifuged, washed, and the pellets counted in a gamma counter. The amount of IL-3 in the tissue culture supernatants was calculated by extrapolating to the linear part of the curve constructed with known amounts of unlabeled IL-3.

RESULTS

Kinetics of IL-3 mRNA induction. The kinetics of IL-3 mRNA accumulation in Jurkat cells following a number of different treatments was examined using RNase protection assays. Detection of β-actin mRNA was included as a
A

Time (h) 0 1 2 4 8 12 16 24
IL-3
\( \beta \)-actin
pSP64
GM-CSF
c-fos

B

Time (h) 0 2 4 8 16 24
IL-3
\( \beta \)-actin
pSP64
GM-CSF
c-fos

C

Time (h) 0 4
IL-3
\( \beta \)-actin
pSP64
GM-CSF
c-fos

D

Time (h) 0 2 4
IL-3
\( \beta \)-actin
pSP64
GM-CSF
c-fos
positive internal control. IL-3 mRNA was not detected in unstimulated Jurkat cells using this assay (Fig 1A) or by the more sensitive polymerase chain reaction (PCR) (results not shown), but was easily detected following PHA stimulation for 4 hours (Fig 1A). Stimulation with PHA together with the calcium ionophore A23187 or PMA resulted in approximately threefold to fivefold greater IL-3 mRNA accumulation after 4 hours than stimulation with PHA alone (Fig 1A). Treatment with A23187 or PMA alone or in combination failed to induce IL-3 mRNA (Fig 1A).

The time course of IL-3 mRNA accumulation over 24 hours of PHA stimulation is shown in Fig 1B. IL-3 mRNA expression was detectable at 2 hours and then increased approximately 3.5-fold to reach a maximum at 6 hours and returned to low levels by 24 hours. Optimal stimulation of Jurkat cells with PHA/PMA induced a similarly transient increase, but IL-3 mRNA was detected at 1 hour and by 6 hours had increased to fivefold higher levels than those observed with PHA alone. A similar profile of IL-3 mRNA accumulation was observed following stimulation of Jurkat cells with PHA and calcium ionophore A23187 (not shown). Stimulation with either PHA, PMA, or A23187 alone had no effect on the levels of β-actin mRNA in these cells.

IL-3 protein was measured in cell culture supernatants to determine if the IL-3 mRNA induced by PHA and PMA stimulation resulted in the production of IL-3 protein. Supernatant samples from stimulated cells were taken at various times and tested by RIA for the presence of IL-3 (Fig 2). No IL-3 was detected in unstimulated cells or in cells treated with cycloheximide for 1 hour before PHA and PHA stimulation. The production of IL-3 protein in stimulated cells closely followed the accumulation of IL-3 mRNA and was detectable as early as 4 hours after PHA stimulation and continued to accumulate in the cell supernatant up to 24 hours. Optimal IL-3 protein levels were obtained after stimulation with PHA/PMA (Fig 2), which induced an approximately 3.5-fold greater increase in the amount of IL-3 detectable in the culture supernatant compared with PHA stimulation alone.

Protein synthesis is required for optimal induction of IL-3 mRNA. We examined the requirement for new protein synthesis in the induction of IL-3 mRNA. Inhibition of protein synthesis with CHX for 1 hour before PHA/PMA stimulation (Fig 3A) resulted in an approximately threefold decrease in accumulated levels of IL-3 mRNA measured 6 hours after stimulation compared with cells stimulated with PHA/PMA (Fig 3B). IL-3 mRNA was not detected in Jurkat cells treated with CHX alone (Fig 3C). In contrast, inhibition of protein synthesis increased the levels of β-actin mRNA over 8 hours (Fig 3A). These data indicate that inhibition of protein synthesis does not superinduce IL-3 mRNA expression and that protein synthesis is required at least in part for the induction of IL-3 mRNA.

IL-3 gene transcription is induced by PHA/PMA and requires new protein synthesis. To determine whether the induction of IL-3 mRNA levels is caused by an increase in the rate of IL-3 gene transcription, nuclear run-on assays were performed. As controls, the transcription rates of β-actin, GM-CSF, and c-fos were also measured. RNase protection assays were used to assess the steady state levels of mRNA in these cells. Although IL-3 mRNA was not detected in unstimulated cells, a low level of IL-3 transcription was apparent (Fig 4A). Stimulation with PHA/PMA induced a transient, approximately ninefold, increase in IL-3 gene transcription (Fig 4A). The rate of transcription reached a maximum at 4 hours after stimulation and then decreased rapidly to prestimulation levels by 6 hours. The steady state IL-3 mRNA level in these cells rose an average of 17-fold over levels detected at 1 hour and reached maximum levels at 6 hours (Fig 4A, and see Fig 1B). Treatment of Jurkat cells with PHA alone induced a lower, approximately 2.5-fold transient increase in IL-3 gene transcription (Fig 4B). GM-CSF gene transcription was also induced by these treatments; however, constitutive transcription above the background level was not detected (Fig 4A through C). The transcription rate of the c-fos gene was variable in many of these experiments. c-fos transcription increased within 1 hour of PMA/PHA stimulation but remained at high levels for several hours after stimulation. The significance of the high-level c-fos transcription in these cells is not clear. Transcription of β-actin remains at a high level and is unaffected by either PMA/PHA or PHA stimulation. In subsequent experiments a gibbon IL-3 cDNA probe, which is 95% homologous to the human IL-3 sequence, was used to determine whether the apparently constitutive transcription observed in unstimulated Jurkat cells was specific for IL-3 coding sequences and not flanking or repetitive sequences that may be present in the genomic probe. Although an overall lower signal was detected with this probe in both stimulated and unstimulated cells, a low level of constitutive transcription of the IL-3 gene was consistently detected (Fig 4C).

To examine the role of protein synthesis in the induction of IL-3 gene transcription, Jurkat cells were treated with CHX for 1 hour before stimulation with PHA/PMA (Fig 4D). This CHX pretreatment abolished the increase in the transcription of IL-3 normally seen following stimulation with PHA/PMA (cf, Fig 4A). However, as shown above, accumulation of steady state IL-3 mRNA in CHX-pretreated cells was detected after PHA/PMA stimulation.
was also greater than 6 hours (not shown). Addition of mRNA before the effects of actinomycin protection assay following inhibition of transcription by actinomycin D treatment. In Jurkat cells treated with PHA alone for 4 hours the IL-3 mRNA had a t_H of approximately 1.5 hours (Fig 5). Maximal stimulation with both PHA and PMA for 4 hours increased the stability of IL-3 mRNA produced in these cells. A small increase in the IL-3 mRNA level was consistently observed in the first 15 minutes after actinomycin D addition to cells treated with PHA/PMA for 4 hours. This increase may reflect accumulation of IL-3 mRNA before the effects of actinomycin D treatment are complete. Under these conditions, IL-3 mRNA has an apparent t_H greater than 6 hours (Fig 5). The t_H of β-actin mRNA in cells stimulated with either PHA or PHA/PMA was also greater than 6 hours (not shown). Addition of CHX for 1 hour before 4 hours of PHA/PMA stimulation also gave a t_H of greater than 6 hours for both IL-3 (Fig 5) and β-actin (not shown). Measurements of IL-3 mRNA t_H after 16 hours of PHA/PMA stimulation showed that as the steady state IL-3 mRNA level in these cells was declining, the mRNA became more unstable having a t_H of approximately 4 hours (Fig 5). Pretreatment with CHX before 16 hours of PHA/PMA stimulation increased the IL-3 mRNA t_H to greater than 6 hours. These data show that IL-3 mRNA produced by stimulation with PHA alone is relatively unstable. PHA/PMA treatment increases the stability of the mRNA, accounting in part for the relatively higher steady state mRNA levels in PHA/PMA-stimulated cells. Protein synthesis appears to be required for the decreased stability of IL-3 mRNA after 16 hours of stimulation, and this decline in mRNA stability may be associated with the decrease in steady state levels of IL-3 mRNA.

**DISCUSSION**

We have investigated the kinetics and the mechanisms of regulation of IL-3 gene expression in the human T-lymphocytic cell line Jurkat. The expression of IL-3 mRNA and protein was detected after stimulation of these cells with PHA. Optimal expression of both IL-3 mRNA and protein was induced by PHA treatment together with a second stimulus, either PMA or the calcium ionophore A23187. Treatment with either PMA or A23187 alone was insufficient to induce IL-3 mRNA accumulation. These results suggest that more than one signal and second messenger pathway may be involved in the regulation and optimal induction of IL-3 expression.

To determine the contribution of PHA- and PMA-stimulation to the expression of IL-3, we examined the effects of these agents on both IL-3 gene transcription and mRNA stability. Surprisingly, although no mRNA was detected in unstimulated Jurkat cells with either RNAse protection assay or PCR, our analysis of the rate of gene transcription in isolated nuclei suggest that the IL-3 gene may be transcribed at a low constitutive level. It is possible that this constitutive transcription may abort before reaching the end of the IL-3 gene; however, no short transcripts have been detected in mRNA from unstimulated cells. The
The physiologic relevance of this constitutive transcription in such a situation is not clear. It may simply indicate that the IL-3 gene is available for transcription and some leakage can occur. The IL-3 gene transcription rate increased transiently by approximately 2.5-fold following stimulation with PHA alone. Recent evidence suggests that the expression of IL-3 in purified T lymphocytes requires the stimulation of a calcium-dependent activation pathway and that stimulation of the T-cell receptor with either anti-CD3 antibodies or PHA may induce expression by elevation of intracellular calcium levels and indirect activation of protein kinase C. Further 3.5-fold increase in the level of expression of IL-3 transcription is apparent following stimulation with PHA/PMA, indicating that PMA as well as PHA may also contribute to the regulation of IL-3 transcription.

Several lines of evidence suggest that the expression of IL-3 mRNA in stimulated Jurkat cells is partially dependent on protein synthesis. Firstly, CHX pretreatment abolished the increase in transcription in stimulated cells but did not block the basal level of IL-3 transcription. Secondly, IL-3 mRNA was not superinduced by CHX treatment alone (Fig 3C). Thirdly, following PHA/PMA stimulation of CHX-pretreated cells, peak levels of IL-3 mRNA were reduced by approximately threefold. The requirement for protein synthesis in induced IL-3 gene transcription may account for this threefold reduction in accumulation of steady state mRNA levels in the presence of CHX. In contrast, both induced transcription and mRNA accumulation of IL-2 in Jurkat cells is completely blocked by prior inhibition of protein synthesis. These data suggest that induction of IL-3 transcription is dependent on synthesis of regulatory proteins.

Using gel mobility shift assays and DNase footprinting techniques, we have mapped binding sites on the IL-3 and GM-CSF promoters for a number of nuclear factors (unpublished results). Some of these factors, eg, NF-GMa, which binds to a sequence, CK1, found in IL-3 and many other HGF genes, appear to be constitutively expressed in T-cell lines and so may contribute to the constitutive IL-3 transcription observed here. Other factors such as AP1 and AP2, which bind to the IL-3 promoter (unpublished results), are inducible by many agents, including PMA, and may be involved in transcriptional induction of IL-3. The role of each of these factors in IL-3 gene transcription is being investigated.

In addition, our results indicate that not only increased transcription but also a modulation of IL-3 mRNA stability may play a role in maximum induction of IL-3 mRNA in stimulated cells. We have investigated the contribution of both PHA and PMA to the increased stability of IL-3 mRNA in stimulated cells. Analysis of the decay rate of IL-3 mRNA in stimulated Jurkat cells showed that at 4 hours after PHA treatment, the half-life of IL-3 mRNA was 1.5 hours. Additional stimulation with PMA together with PHA produced a marked increase in IL-3 mRNA stability with little appreciable decay over a 6-hour period. Therefore, the role of PMA may be mediated mainly through stabilization of existing mRNA because it alone, unlike PHA, cannot induce IL-3 gene transcription. Similar increases in GM-CSF mRNA stability following PMA stimulation have also been observed. At 16 hours poststimulation, when steady state levels of mRNA are decreasing, the stability of the IL-3 mRNA has also decreased. Pretreatment with CHX prolongs the increased stability of IL-3 mRNA and suggests that a labile RNAse may be involved in the specific degradation of IL-3 mRNA. Thus, modulation of the stability of IL-3 mRNA may serve to limit the expression of IL-3 in resting T lymphocytes and to augment rapid accumulation of mRNA during cell activation.

In summary, both transcriptional and posttranscriptional mechanisms are involved in the regulation of IL-3 expression in human T cells. Our experiments suggest that, despite a low constitutive level of transcription in unstimulated cells, steady state levels of IL-3 mRNA are maintained at undetectable levels, probably by rapid mRNA destruction. Whether constitutive transcription and posttranscriptional processing of the IL-3 mRNA in Jurkat cells is a reflection of their transformed phenotype or whether these mechanisms operate in other cell types remains to be determined. Low level transcription might allow the steady low-dose delivery of IL-3 in the bone marrow in keeping with its suggested role of maintaining steady state hematopoiesis. In situations where high doses of IL-3 may be needed, induction of IL-3 expression is achieved by both increasing gene transcription, presumably by induction of one or several transcription factors, and by stabilizing the newly synthesized IL-3 mRNA.

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