Activation of Apoptosis Associated With Enforced Myc Expression in Myeloid Progenitor Cells Is Dominant to the Suppression of Apoptosis by Interleukin-3 or Erythropoietin

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The inappropriate expression of c-myc in cells deprived of growth factors has recently been implicated in the activation of programmed cell death (apoptosis). The studies described here examine the ability of interleukin-3 (IL-3) or erythropoietin (Epo) to suppress apoptosis that occurs in association with enforced myc expression during cell cycle arrest of a murine IL-3-dependent myeloid progenitor cell line, 32D. G1 arrest was observed when culturing 32D cells to high density in medium supplemented with IL-3, or at subconfluent densities in medium supplemented with Epo. Under both conditions, endogenous c-myc expression was downregulated and viability was maintained. In clones of cells in which c-myc is constitutively expressed from a retroviral vector, enforced c-myc expression was associated with the activation of apoptosis at high cell densities. Similarly, enforced c-myc expression was deleterious to cell survival when these cells were cultured in Epo, as apoptosis was evident within 6 hours. The results support the concept that inappropriate c-myc expression activates apoptosis and that neither IL-3 nor Epo can suppress this program under these conditions.

The induction of c-myc gene expression is an immediate early response to diverse mitogenic stimuli, and c-myc expression is decreased in response to growth factor deprivation or growth inhibitory agents. This regulation is frequently disrupted in neoplastic cells, and the increased incidence of hematopoietic malignancies in Myc transgenic mice has clearly shown that such deregulation contributes to carcinogenesis. Although the precise biochemical function of c-myc has remained elusive, several lines of evidence indicate that downregulation of c-myc expression is a required event for cells to withdraw from the cell cycle and enter either a differentiation program or a quiescent state. Enforced c-myc expression drives cell cycle progression and blocks differentiation of several cell types. Conversely, reducing c-myc levels using antisense constructs blocks progression into S phase and promotes differentiation. Myc contains several domains common among transcription factors and, in conjunction with its heterodimeric partner Max, has been shown to possess sequence specific DNA binding activity and to activate transcription from heterologous promoters. Therefore, it is believed that Myc activates the transcription of genes involved in cell cycle progression, although clear evidence for this has been difficult to obtain. Recently, Myc has also been implicated in the activation of novel signal transduction pathways involved in programmed cell death (apoptosis). Apoptosis plays an important role in the regulation of hematopoiesis by deleting growth factor-dependent progenitor cells in response to physiologic reductions in hematopoietins. However, little is known about the genes involved in this signaling pathway.

We have previously shown that c-myc is an immediate early response gene after interleukin-3 (IL-3) stimulation of IL-3-dependent myeloid progenitor cell lines. The expression of c-myc in these cells is rapidly downregulated on withdrawal of IL-3, and this is followed by a progressive and synchronous accumulation of cells at an early point in the G1 phase of the cell cycle. By enforcing c-myc expression using a retroviral vector, we showed that failure to downregulate c-myc expression in response to IL-3 deprivation prevented these cells from undergoing G1 arrest and accelerated programmed cell death. The rapid onset of apoptosis suggested that the induction of apoptosis was an immediate response to the inappropriate expression of c-myc in the absence of growth factor. Similar observations have been made in fibroblasts, where inducible c-myc expression was associated with the induction of apoptosis after serum deprivation. This effect was dependent on the expression of Myc protein, and was not observed in cells expressing forms of myc that contain mutations in domains required for co-transformation, autoregulation, and inhibition of differentiation.

Current evidence indicates that hematopoietic growth factors suppress apoptosis in growth factor-dependent cells, and that this viability-promoting activity is distinct from effects on cell cycle progression. Moreover, it has recently been shown that IL-3 suppresses the apoptosis that is induced in myeloid progenitor cells exposed to X-irradiation or to the cytotoxic drugs etoposide and cisplatin. Therefore, analysis of the effects of constitutive c-myc expression under conditions of starvation-induced growth arrest is complicated by the fact that IL-3 deprivation removes this apoptosis-suppressing activity. For this reason we were interested in studying the consequences of c-myc deregulation in situations where cells undergo growth arrest in the presence of hematopoietins that have been shown to promote cell survival by suppressing apoptosis. In this report we show that enforced c-myc expression is lethal to cells under conditions in which normal cells undergo cell...
cycle arrest in the presence of either IL-3 or erythropoietin (Epo). Failure to downregulate \textit{c-myc} expression, even in the presence of hematopoietins that promote cell survival, is therefore associated with the onset of apoptosis.

**MATERIALS AND METHODS**

\textbf{Cell culture}. The 32Del3 cell line (kindly provided by Dr G. Rovera, the Wistar Institute, Philadelphia), is an IL-3-dependent, non-tumorogenic myeloid cell line derived from normal marrow.\textsuperscript{10} This cell line has an undifferentiated phenotype and a diploid karyotype.\textsuperscript{11,12} A subclone of this cell line (32D.3) was used in this study. Cells were grown in RPMI-1640 medium (Whitaker Bioproducts, Inc, Walkersville, MD) supplemented with 10\% fetal calve serum (FCS) (Hyclone, Logan, UT), L-glutamine, and 20 U/mL of high performance liquid chromatography (HPLC)-purified murine IL-3.\textsuperscript{1-4} The fpGVc-\textit{myc} retrovirus has been previously described.\textsuperscript{7} The virus contains exons 2 and 3 of the murine \textit{c-myc} gene but differs from the endogenous gene in the 3' untranslated region that allows distinction between endogenous and virus-expressed \textit{c-myc} mRNA. Four clones of \textit{c-myc} retrovirus-infected 32D.3 cells (\textit{myc} 1-4) that constitutively express the exogenous \textit{c-myc} gene were previously described.\textsuperscript{7} All \textit{c-myc} clones contain unique fpGVc-\textit{myc} virus integration sites as assessed by Southern blot analysis (data not shown). Cell viability was assessed using trypan blue dye exclusion.

\textbf{Determination of cell cycle distributions}. To assure that cultures were initiated at the same phase of growth, 24 hours before the experiment cells were plated at \(3 \times 10^5\) cells/mL. Twenty-four hours later, cells were seeded at \(1 \times 10^5\) cells/mL in medium supplemented with 100 U/mL HPLC-purified IL-3. Cultures were supplemented with an additional 100 U/mL IL-3 on day 4 to prevent any loss of IL-3 activity associated with prolonged culture. At the time points indicated the cell cycle distributions of propidium-iodide-stained cells were determined by analysis with the computer program PEAK as described in Materials and Methods. (---), fraction in G1. (••••), fraction in S. (-----), fraction in G2M.

![Graph showing cell cycle distributions](image-url)

**Fig 1. Changes in cell-cycle distribution associated with increasing cell density**: The indicated cell lines were seeded at \(1 \times 10^5\) cells/mL in an excess of HPLC-purified IL-3 (100 U/mL) and harvested for cell-cycle analysis after 1 (Day 1) or 6 (Day 6) days in culture. Cultures were supplemented with an additional 100 U/mL of IL-3 on day 4 to prevent any loss of IL-3 activity associated with prolonged culture. Cells were harvested for cell cycle analysis after 1 and 6 days of culture. The doubling time for this cell line is 27 hours. For determination of cell cycle distributions in the presence of Epo, cultures were washed of IL-3 and seeded at \(5 \times 10^5\) cells/mL in the presence of 10 U/mL recombinant human Epo (Amgen, Thousand Oaks, CA). All cells were collected at each time point by centrifugation and resuspended in 0.1 Fg/mL ethidium bromide. In experiments addressing the effects of Epo on apoptosis, cells were washed and resuspended in 0.1% sodium citrate containing 50 \(\mu\)g/mL propidium iodide. Fluorescence of propidium-iodide-stained cells was measured as previously described\textsuperscript{7} using an EPICS 753 flow cytometer (Coulter Corp, Hialeah, FL). Nuclei from dead cells containing less than 2N DNA were gated from the analyses. Cell-cycle analysis was performed using the computer program PEAK.\textsuperscript{7}

\textbf{Electrophoretic analysis of oligonucleosomal DNA degradation (apoptosis)}. In experiments addressing the onset of apoptosis during logarithmic growth, cells were seeded into RPMI-1640/10\% FCS supplemented with 100 U/mL IL-3 at \(2 \times 10^5\) cells/mL. After various incubation times, total cellular DNA was isolated from \(1 \times 10^6\) cells as previously described\textsuperscript{7} and loaded into the dry wells of a 2\% agarose gel containing 0.1 \(\mu\)g/mL ethidium bromide. In experiments addressing the effects of Epo on apoptosis, cells were washed of IL-3 and resuspended in RPMI-1640/10\% FCS supplemented with 10 U/mL of Epo. After 6 and 14 hours incubation, total cellular DNA was isolated and electrophoresed as indicated above.

\textbf{RNA analysis}. Total RNA was isolated from cells by extraction in guanidinium isothiocyanate and pelleting through a cesium chloride gradient as previously described.\textsuperscript{24} For Northern analysis, 20 \(\mu\)g of total RNA was electrophoresed on 1\% agarose/6\% formaldehyde gels, transferred to nitrocellulose, and hybridized under stringent conditions to \(32\text{P}-\)labeled nick-translated DNA probes. The follow-
Results

Regulation of c-myc expression during density-dependent G1 arrest in IL-3. The kinetics of c-myc downregulation and G1 arrest were studied during density-dependent growth inhibition of 32D.3 cells cultured in the presence of IL-3. To evaluate the ability of this cell line to arrest at confluence, cells were seeded in an excess of IL-3 (100 U/mL) and harvested for cell cycle analysis after 1 and 6 days of culture. Cultures were supplemented with an additional 100 U/mL of IL-3 on day 4 to prevent any loss of IL-3 activity associated with prolonged culture. As illustrated in Fig 1, after 1 day of culture 32D cells displayed a cell-cycle distribution typical of logarithmically growing cells, but by day 6 there was a significant increase in the fraction of cells in G1, and a concomitant decrease in the proportion of cells entering S-phase. This period corresponded to the peak of the growth curve (see below, Fig 4A), suggesting that the cultures were undergoing growth arrest at these densities.

Therefore, the ability of 32D cells to arrest at confluence provided an opportunity to further explore the association between G1 arrest and the induction of apoptosis by constitutive c-myc expression. We have previously generated four unique subclones of the 32D.3 cell line that constitutively express the murine c-myc gene from a retroviral vector. All c-myc clones failed to achieve the same degree of G1 arrest as parental cells after 6 days of culture (Fig 1), suggesting that they were continuing to progress through the cell cycle. In support of this, the height of the curve at the entry point into S-phase remained elevated in all c-myc clones, but had significantly decreased in parental 32D.3 cells (Fig 1). This indicated that, in contrast to parental cells, c-myc clones were continuing to progress into S phase at this time in culture. Representative data is shown for control 32D.3 cells and two myc subclones (myc2 and myc4).

Because c-myc expression is tightly linked to cell proliferation, we examined the effects of density-dependent growth arrest on the levels of c-myc mRNA. Total RNA was isolated from aliquots of cells treated as shown in Fig 1, and examined for levels of c-myc mRNA by Northern blot analysis. In 32D.3 cells, endogenous c-myc expression was downregulated as the cells approached confluence (Fig 2, lanes 3 and 4, corresponding to days 4 and 6 of growth, respectively). This was not caused by depletion of IL-3 or other nutrients because conditioned medium from dense cultures could still support log-phase growth of control 32D.3 cells (data not shown). Levels of transcripts for ODC were also downregulated by increasing cell density, consistent with current data indicating that myc influences expression of this gene. The level of transcripts for the heterodimeric partner of c-myc, max, did not fluctuate with time in culture. The exogenous c-myc gene was constitutively expressed in all four c-myc clones (data for the myc2 clone shown in Fig 2), thereby preventing any density-dependent downregulation of c-myc mRNA. ODC RNA levels did not decrease in c-myc clones with continued cell growth, presumably reflecting the constitutive expression of c-myc in these cells.

Failure to downregulate c-myc expression at confluence is associated with the activation of apoptosis. To determine if enforced c-myc expression was associated with activation of apoptosis at high cell densities in IL-3-supplemented cultures, cells seeded at 2 × 10^5 cells/mL in complete medium with 100 U/mL IL-3 were allowed to grow for 3 consecutive days. The integrity of genomic DNA in cells harvested on each day was then analyzed by agarose gel electrophoresis. As shown in Fig 3, DNA degradation was undetected in control cells throughout the experiment. However, both
myc clones showed the classic oligonucleosomal ladder of DNA degradation characteristic of apoptosis by the third day, indicating the premature onset of programmed cell death in these cultures. Corroborative morphologic evidence of apoptosis (cytoplasmic membrane blebbing and chromatin condensation) was apparent in myc clones examined at this point in culture (data not shown).

**Constitutive expression of c-myc is lethal to cells growing at high cell densities.** Because c-myc clones were susceptible to apoptosis with prolonged culture in IL-3 (Fig 3), yet continued to show evidence of entry into S-phase (Fig 1), a growth curve was initiated for control 32D.3 cells, a clone containing the control fpGV vector (GV1.1), and all myc clones. Cells were harvested daily and evaluated for viable cell number (Fig 4A) and percent viability (Fig 4B). All four c-myc clones lost cell viability at densities between 1 and 2 × 10⁶ cells/mL (Fig 4A and B). Viability showed a rapid decline between 48 and 96 hours and progressed rapidly to the
death of the cells (Fig 4B), despite the fact that the cultures were supplemented with an excess of IL-3. Therefore, IL-3 was unable to promote the survival of c-myc clones at high cell densities. This was in marked contrast to control cells, which maintained their viability over more than 96 hours and at densities greater than 2 × 10^6 cells/mL. Loss of viability in the c-myc clones was spread out over several days, consistent with previous reports that induction of apoptosis appears to be a stochastic process.21 The few cells that remained viable at the later time points continued to show evidence of progression into S-phase (Fig 1), and eventually died.

**Epo promotes survival of 32D cells deprived of IL-3.** To determine if the lethal effect of constitutive c-myc expression was restricted to cells growing in IL-3, we examined the effects of Epo in the absence of IL-3. 32D.3 cells express low numbers of Epo receptors (approximately 70 per cell) and low levels of Epo-receptor transcripts (data not shown). Supplementing IL-3-deprived 32D cells with Epo significantly delayed the onset and rate of cell death, and extended the viability of these cells for several days (Fig 5). Cells that had extended survival in Epo were arrested in the G1 phase of the cell cycle (Fig 6). However, this G1 block was completely reversible because the addition of IL-3 to G1-arrested cultures stimulated G1 progression and long-term growth (data not shown). This indicates that in these cells Epo stimulation provides a survival function, but is unable to promote cell-cycle progression.

**Regulation of c-myc expression by Epo.** We next tested the effects of Epo stimulation on c-myc expression. C-myc transcript levels rapidly diminished after removal of IL-3 from 32D cell cultures (Fig 7). When Epo was added to IL-3-deprived cells, c-myc transcript levels showed the same initial downregulation. However, this was followed by a reinduction at 16 hours (Fig 7). This regulation of c-myc RNA levels is clearly evident when one compares the 8 and 24 hour +Epo lanes, where significant fluctuations of c-myc transcripts occur even though β-actin and max transcript levels remain constant. A similar downregulation of c-myc transcripts, followed by reinduction, has been previously reported in murine erythroleukemia cells (MEL) induced to undergo erythroid differentiation with dimethylsulfoxide.8,10 However, we were unable to detect any evidence of erythroid differentiation in 32D cells after Epo stimulation, as determined by morphology (data not shown) and the absence of Band 3 or β-globin expression (Fig 7). Neither IL-3 deprivation nor Epo stimulation had any effect on the steady-state levels of transcripts for max.

**Epo fails to support survival of 32D cells that constitutively express c-myc.** Downregulation of c-myc expression followed by G1 arrest in Epo provided an additional system to address the consequences of deregulated c-myc expression in response to signaling pathways that promote viability in the absence of proliferation. Although Epo receptor transcript levels were comparable in c-myc clones and control cells (data not shown), Epo failed to support the viability of the c-myc clones. C-myc clones rapidly lost viability with kinetics similar to IL-3-deprived cells (Fig 5). To address whether accelerated death of myc clones in Epo was associated with apoptosis, genomic DNA was isolated from cultures deprived of IL-3 and from those supplemented with Epo. Genomic DNA degradation characteristic of apoptosis was detected within 6 hours in both IL-3-deprived (Fig 8C) and Epo-supplemented (Fig 8A) c-myc clones; by 14 hours virtually all of the high molecular weight DNA in IL-3-deprived (Fig 8D) or Epo-supplemented (Fig 8B) c-myc clones was degraded into oligonucleosomal fragments. Morphologic evidence of apoptosis was also clearly evident in these cultures (data not shown). The rapid onset of apoptosis in c-myc clones stimulated with Epo correlated with the drop in c-myc transcript levels during the first 8 hours of Epo stimulation (Fig 7). By contrast, treatment of control 32D.3 cells with Epo delayed the onset of apoptosis as analyzed by DNA degradation, which is detectable 14 hours after IL-3 deprivation (Fig 8D), but not in 32D.3 cells supplemented for the same interval with Epo (Fig 8B).

**DISCUSSION**

Several mechanisms control the rates of self-renewal and differentiation of bone marrow (BM)-derived stem cells. In steady-state BM, the stem cell pool is in a G0 state, although it can be stimulated to enter the cell cycle in response to a
physiologic demand for an increase in mature blood cell numbers. The ability of hematopoietic stem cells to survive in the G0 phase of the cell cycle has been shown to be independent of known hematopoietic growth factors,34 but the survival of differentiating progenitor cells requires the presence of one or more hematopoietic growth factors throughout most of their lifespan.35 Therefore, the regulation of progenitor cell turnover is accomplished, at least in part, by the activation of an endogenous program of cell suicide, or apoptosis, in response to a physiologic reduction in hematopoietic growth-factor levels.23,25,26

We have previously shown that enforced c-myc expression in myeloid progenitor cells deprived of IL-3 is associated with accelerated apoptosis.7 Because an important aspect of cellular growth control by hematopoietic growth factors involves signals that ensure cell survival,25-28 it is reasonable to assume that IL-3-deprived cells no longer express the genes that are required to promote viability. Therefore, we were interested in examining whether apoptosis would also be associated with enforced myc expression if hematopoietic cells were undergoing G1 arrest in the presence of specific hematopoietins that promote cell survival. To address this we chose to study two forms of growth arrest that occur in an IL-3-dependent myeloid progenitor cell line: (1) density-dependent G1 arrest in the presence of IL-3; and (2) G1 arrest in the presence of Epo.

We have shown that, in the presence of IL-3, 32D.3 cells downregulate c-myc expression and accumulate in G1 as they approach confluence. The degree of G1 arrest observed was not as extensive as one would see in a culture of fibroblasts. This is presumably caused by the fact that 32D cells grow in suspension culture, and are therefore less susceptible to cell-cell interactions that restrict the growth of monolayer cultures. Nevertheless, when c-myc expression was en-

Fig 6. The effects of Epo on cell-cycle progression. Control 32D.3 cells were seeded at 5 x 10⁵ cells/mL in medium containing 10 U Epo/mL and no IL-3, and harvested for cell cycle analysis after overnight (16 hr), 2 days (2D), and 6 days (6D) of culture as described in Materials and Methods. (-- --), fraction in G1. (-----), fraction in S. (-------), fraction in G2M.
Myc OVERRIDES SUPPRESSION OF APOPTOSIS BY IL-3

Fig 7. Regulation of gene expression in response to Epo stimulation. RNA was isolated from aliquots of 32D cells deprived of IL-3 (− IL-3) or deprived of IL-3 and stimulated with Epo (− IL-3 + Epo) after incubation for the indicated number of hours. RNA from each time point was transferred to nitrocellulose after electrophoresis, and hybridized to probes specific for c-myc, max, β-actin, Band 3, and β-globin as described in Materials and Methods. RNA derived from murine BM or day 18 gestation murine fetal liver was used as a positive control for hybridization to the Band 3 and β-globin probes.

forced in these cells, they failed to undergo the G1 arrest characteristic of parental cells, indicating that constitutive c-myc expression deregulated cell-cycle controls. The constitutive expression of c-myc was not detrimental to the viability of these cells as long as they were in logarithmic growth (Fig 4). Indeed, all c-myc clones were indistinguishable from the parental clone with respect to their doubling time. The deleterious effect of enforced c-myc expression, illustrated by the rapid onset of apoptosis, only becomes evident when cells are undergoing G1 arrest, a condition that is associated with the downregulation of c-myc expression (Fig 2). Therefore, the inappropriate expression of c-myc during density arrest is associated with apoptosis in these cells. Moreover, because apoptosis occurred in the presence of an excess of IL-3, this suggests that apoptosis in c-myc clones cannot be suppressed by IL-3, even though this ligand clearly suppresses apoptosis in myeloid progenitors.25

Similar results were observed during G1 arrest in the presence of Epo. Although 32D.3 cells are IL-3-dependent, their viability can be maintained for several days in the absence of IL-3 if the cultures are supplemented with Epo. Epo stimulation was associated with a period of c-myc downregulation that was followed by a reinduction. A similar pattern of c-myc regulation is seen in MEL cells after induction of erythroid differentiation by dimethylsulfoxide.8,10 However, unlike MEL cells 32D.3 cells did not undergo erythroid differentiation. Importantly, the enforced expression of c-myc during Epo stimulation was associated with the rapid onset of apoptosis during the period when the endogenous gene is downregulated. This indicates that apoptosis in c-myc clones cannot be suppressed by Epo, even though this ligand does support survival (Fig 5) and suppresses programmed cell death of parental 32D.3 cells (Fig 8B).

Evidence for an association between inappropriate c-myc expression and the activation of apoptosis has been obtained from several systems. First, in the rat ventral prostate, the removal of hormone induces the expression of a number of immediate early response genes before the onset of apoptosis, one of which is c-myc.36 Second, antisense c-myc oligonucleotides inhibit apoptosis after T-cell receptor gene activation.23 Third, in fibroblast tumors induced with myc-containing retroviruses, there is a high percentage of tumor cells undergoing programmed cell death.37 Fourth, the onset of apoptosis in fibroblasts after the induction of myc expression has been shown to be associated with specific domains required for Myc function.21 Finally, we have shown that enforced myc expression is tightly associated with activation of apoptosis in either ligand-deprived or growth factor-supplemented myeloid progenitor cells. This is in contrast to parental 32D cells, where analysis of multiple time points after IL-3 withdrawal indicates that apoptosis is evident only when endogenous c-myc expression has declined to almost undetectable levels (eg, see Fig 7 and 8D). This indicates that there are multiple, yet distinct, signaling pathways that culminate in activation of the suicide program.

The p53 tumor suppressor gene is the only other gene that has been shown to be associated with activation of apoptosis in hematopoietic cells. The myeloid leukemia cell line M1 is deficient in wild-type p53 expression and was shown to undergo apoptosis when the wild-type p53 was introduced into these cells.38 Because both wild-type p53 and c-myc influence cell cycle regulation, this may indicate that other abnormalities in cell cycle control are similarly deleterious for cell survival.

Despite the ability of c-myc to promote cell-cycle progression, it appears that a deregulated c-myc gene is associated with activation of apoptosis under diverse conditions that act to depress the proliferative activity of hematopoietic progenitor cells. Such a system provides an effective means to select against mutant cells that fail to respond to growth arrest signals. Because c-myc activation is so widespread in neoplastic diseases, the apparent paradoxical effects of myc
3.1  7  1.0  - 2.0  1.6  0.5  0.3

Fig 8. Analysis of apoptosis in cultures stimulated with Epo. 32D cells and the four myc clones were washed of IL-3, and cultured in either in the absence of IL-3 (C and D), or in IL-3–free medium supplemented with Epo (A and B). Genomic DNA was isolated after incubation for 6 hours (A and C), or 14 hours (B and D) and analyzed by electrophoresis as described in Materials and Methods.

on promoting cell-cycle progression and compromising cell survival suggests that cells harboring deregulated c-myc genes must express additional genes that can suppress apoptosis. In support of this concept, bcl-2 expression has been shown to suppress apoptosis that is associated with inappropriate myc expression in both fibroblasts and T-cells. Therefore, it is conceivable that other genes that converge on apoptosis-signaling pathways may also contribute to tumorigenesis by cooperating with an activated c-myc gene.

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Myc OVERIDES SUPPRESSION OF APOPTOSIS BY IL-3


Activation of apoptosis associated with enforced myc expression in myeloid progenitor cells is dominant to the suppression of apoptosis by interleukin-3 or erythropoietin

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