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Transcriptional and Posttranscriptional Control of c-*myc* Gene Expression in WEHI 231 Cells

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Incubation of WEHI 231 cells, derived from a murine B-cell lymphoma, with antisera directed against its surface immunoglobulin results in the inhibition of growth within 24 h. Previously, we demonstrated that this treatment selectively affects cytoplasmic levels of c-*myc* mRNA (J. E. McCormack, V. H. Pepe, R. B. Kent, M. Dean, A. Marshak-Rothstein, and G. E. Sonenshein, Proc. Natl. Acad. Sci. USA 81:5546–5550, 1984). An initial increase in the cytoplasmic mRNA level is followed by a precipitous drop. We now show that the early increase results from a dramatic increase in the rate of c-*myc* gene transcription, as well as from partial stabilization of the mRNA in the cytoplasm. The later decrease results from a shutdown in transcription of the c-*myc* gene and a return to the normal lability of the cytoplasmic c-*myc* mRNA. Treatment with phorbol ester, like treatment with anti-immunoglobulin sera, inhibited WEHI 231 cell growth and caused similar changes in cytoplasmic c-*myc* mRNA levels, which can also be related to alterations in c-*myc* gene transcription. These results indicate that the control of c-*myc* gene expression in B cells is effected through regulation at multiple levels.

The c-*myc* proto-oncogene is a normal cellular gene which is expressed in all tissue types examined (3). The c-*myc* protein has been localized to the nucleus (17), although its function is not known. We and others have shown that in lines of nontransformed murine fibroblast cells, the level of c-*myc* mRNA is low during quiescence and that it increases 10- to 30-fold early during the G_0-to-G_1 transition as the cells begin proliferation (7, 20). Similarly, c-*myc* mRNA levels are low in adult rat liver and increase dramatically following partial hepatectomy (14, 23). On the other hand, terminal differentiation of F9 teratocarcinoma cells to nonproliferating endoderm cells is accompanied by a decrease in expression of c-*myc* mRNA (7). These results point to a role for the c-*myc* gene in control of cell proliferation. Perturbations of the c-*myc* locus have been documented for many B-cell malignancies of human, mouse, and chicken origin, including nearby integration of a retrovirus (18), point mutations (27), and chromosomal translocations (1, 30, 32). In most of these cases, the coding region for the c-*myc* protein product would not be affected by these changes. This leaves open the possibility that these alterations lead to changes in the regulation of c-*myc* expression; such altered regulation is then implicated in the development of the neoplastic state.

WEHI 231 is a murine lymphoma cell line that has been characterized as an early B cell on the basis of surface markers and biological properties (28). Although these cells are transformed, the c-*myc* genes are unrearranged in this line, and these cells remain capable of responding to various immunological stimuli in a manner reminiscent of that of nontransformed cells. For example, they express surface immunoglobulin M while secreting only very low amounts of immunoglobulin into the medium. Treatment of WEHI 231 cells with an antiserum against mouse immunoglobulin inhibits their proliferation (5). The growth inhibition has been shown to be mediated specifically by binding of antibody to the surface immunoglobulin M (5). Immunoglobulin-treated cells undergo one round of division, and further proliferation is inhibited. Cessation of DNA replication occurs within 24 to 48 h (5, 24).

In previous studies, we used the WEHI 231 cell system to monitor changes in c-*myc* gene expression accompanying cessation of B-cell proliferation (24). Following incubation of cultures of exponentially growing WEHI 231 cells with goat anti-mouse immunoglobulin antiserum (GaMIg), there was a rapid increase in the amount of c-*myc* mRNA during the first 2 h. Then the level dropped precipitously, to 5- to 10-fold lower than control values by 6 h. In contrast, the amounts of most major mRNAs, including μ heavy chain and actin, were only slightly altered even 24 h after GaMIg exposure. In the period between 2 and 4 h after treatment, c-*myc* mRNA decayed with a half-time of 20 to 30 min. We have now examined the effect of GaMIg treatment on the regulation of c-*myc* gene expression in WEHI 231 cells. Rapid changes in both the rate of c-*myc* gene transcription and the rate of decay of c-*myc* mRNA occurred.

Rapid induction of c-*myc* cytoplasmic RNA by anti-immunoglobulin antiserum treatment. We previously showed that treatment of WEHI 231 cells with GaMIg alters the expression of c-*myc* genes in WEHI 231 cells within 2 h (24). Figure 1 displays an RNA blot analysis for c-*myc*-specific sequences within cytoplasmic RNA isolated from control cells or cultures treated with GaMIg for 2, 4, 8, or 24 h. Levels of c-*myc* RNA were elevated 10- to 20-fold at 2 h after treatment and declined rapidly thereafter. By 8 h, c-*myc* RNA levels were below those found in exponentially growing cells, and the levels declined even further by 24 h.

To quantitate c-*myc* RNA levels at earlier times, we isolated cytoplasmic RNA at 15, 30, 60, and 120 min following GaMIg treatment and analyzed it as described above. Levels of c-*myc* RNA increased within 30 min of treatment and continued to increase rapidly until 1 h (Fig. 1). The rapid increase in c-*myc* RNA levels was not the result of a generalized increase in cytoplasmic mRNA, since the amount of histone H3.2 RNA remained relatively constant

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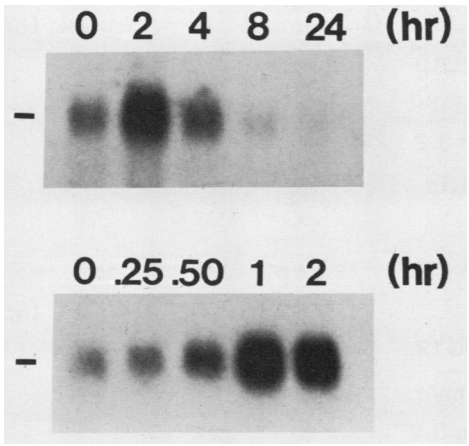

FIG. 1. Rapid changes in the level of cytoplasmic c-*myc* mRNA following GaMIg treatment. Equal amounts of cytoplasmic RNA (15 μg) from control or immunoglobulin-treated WEHI 231 cells were isolated at the indicated times and analyzed by Northern blot hybridization (22) to ^{32}P-labeled c-*myc* DNA probe (13). For Northern blots, the 5.5-kilobase *Bam*HI genomic fragment of the S107 mouse myeloma containing exons 2 and 3 of c-*myc* (21) was used.

during this period (data not shown). In addition, as described previously (24), analysis of the cell-free translation products of mRNA isolated from untreated cultures or cultures treated with GaMIg for 2, 6, or 24 h showed that they were essentially identical. Thus the level of c-*myc* mRNA undergoes a rapid and selective increase and decrease following treatment of WEHI 231 cells with antiserum against surface immunoglobulin M.

Stability of cytoplasmic c-*myc* mRNA. It is well documented that c-*myc* gene expression can be regulated at the level of mRNA stability (8, 9). The disappearance of c-*myc* mRNA in the WEHI 231 cells following 2 h of GaMIg treatment is rapid, occurring with a half-time of less than 30 min. This value is similar to the normal half-life of c-*myc* mRNA in mammalian cells (8, 26). To determine whether enhanced mRNA stability is responsible for the rapid increase in c-*myc* mRNA levels during the first 2 h of treatment, we measured mRNA decay rates in control cells and in cultures treated with GaMIg for 10 min or 2 h. Decay of c-*myc* mRNA in control cultures occurred with a half-time of 10 to 15 min in the presence of 2 μg of actinomycin D per ml (29) (data not shown). A similar value has been reported for other mouse and human cell lines (8, 26). In cells treated with GaMIg for 10 min, the rate of decay of c-*myc* mRNA following inhibition of transcription was significantly lower (Fig. 2); a half-life of approximately 25 min was obtained. The failure of the c-*myc* mRNA levels to increase past the 10-min GaMIg time point indicates that the actinomycin D treatment was effective in blocking transcription. The decay of c-*myc* mRNA in cultures treated with GaMIg for 2 h is shown in Fig. 2. Densitometric analysis of lighter exposures of this autoradiogram (Fig. 2) indicates that c-*myc* mRNA disappeared with kinetics that were essentially identical to those of control cultures: a half-life of 10 to 12 min was observed. Similar changes in c-*myc* mRNA stability were observed when cells were incubated with 30 μg of 5,6-dichlorobenzimadazole riboside, another inhibitor of transcription, per ml (data not shown). Therefore, following treatment of cells with GaMIg, there was an early, transient decline in the rate of c-*myc* mRNA turnover.

c-*myc* RNA is regulated transcriptionally. To see whether the rate of synthesis of c-*myc* mRNA might also change after treatment with GaMIg, we assessed the rates of c-*myc* gene transcription over the time course. Nuclei were isolated at 1, 2, 4, 8, and 24 h following GaMIg treatment, and c-*myc* run-on transcription assays were performed essentially as described by Greenberg and Ziff (15) (Fig. 3). GaMIg induced a 7- to 12-fold increase in c-*myc*-specific transcription within 1 h of treatment. After this time, specific transcription of c-*myc* genes declined rapidly and was barely detectable by 8 h of treatment. Similar results were obtained with an M13 single-strand DNA probe for the transcribed sense strand of the c-*myc* gene (data not shown).

To monitor the kinetics of the early events, we isolated nuclei following 15, 30, 60, and 120 min of GaMIg treatment and analyzed them as described above (Fig. 3). Transcription of c-*myc* genes began to increase between 15 and 30 min and reached a maximal level after approximately 1 h of treatment. Actin transcription was also induced by incubation with GaMIg; however, the kinetics of induction were different. Transcriptional activation of actin occurred within 15 min of treatment, peaked by 30 min, and declined to pretreatment levels by 2 h.

c-*myc* is regulated by phorbol esters. The kinetics of c-*myc* and actin transcriptional activation in WEHI 231 cells are strikingly similar to those found for quiescent mouse fibroblasts stimulated by serum or growth factor addition (7, 15,

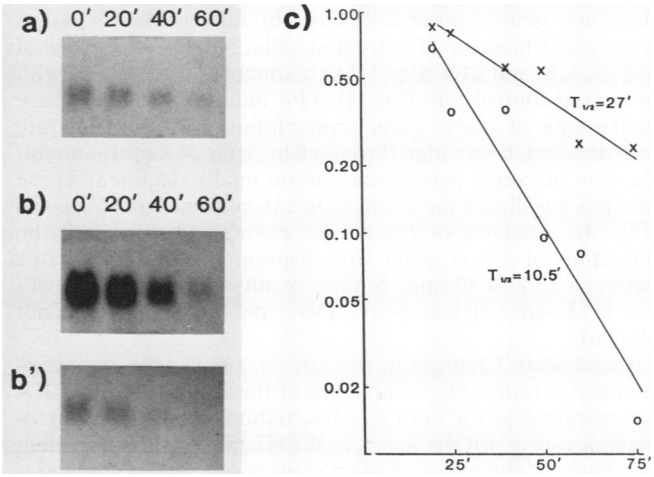

FIG. 2. Transient stabilization of c-*myc* mRNA following GaMIg treatment. Following incubation of cultures of exponentially growing WEHI 231 cells with GaMIg for 10 min or 2 h, actinomycin D was added to a final concentration of 2 μg/ml. (Incorporation of [^{3}H]uridine [1 μCi/ml, 36 Ci/mmol] into trichloroacetic acid-insoluble material during a 30-min pulse period was reduced by 98% at both time points by the presence of actinomycin D.) Aliquots of the cultures were then removed at 0, 20, 40, or 60 min, cytoplasmic RNA was extracted, and the decay of c-*myc* mRNA was assessed by Northern blotting (10 μg per lane). (a) Pretreatment for 10 min with GaMIg. (b) Pretreatment for 2 h with GaMIg. (b') Shorter exposure of autoradiogram shown in panel b. (c) Quantitative analysis. The blots shown in panels a, b, and b', along with autoradiograms produced in parallel experiments, were subjected to scanning densitometry to determine relative levels of c-*myc* mRNAs; within each set of samples, values were normalized to 1.00 at $T = 0$ min. The data were plotted on a semilog graph, and the line of best fit was determined by the method of least squares, omitting the 0-min time point to account for the fact that actinomycin D does not act instantaneously upon addition. Symbols: ×, 10-min GaMIg treatment; ○, 2-h GaMIg treatment.

20). Many of the events which follow serum stimulation of quiescent fibroblasts and activation of normal B and T cells involve protein kinase C (6, 25). To determine whether a similar pathway is functioning in WEHI 231 cells and whether its activation ultimately inhibits cell growth, we treated cells with the phorbol ester TPA (12-O-tetradecanoylphorbol-13-acetate), a potent activator of protein kinase C. Initial growth studies indicated that 5×10^{-8} M TPA inhibited DNA synthesis and cell growth within 24 to 48 h of treatment (data not shown). In addition, the formation of large cellular aggregates, which are characteristic of GaMIg-treated cells, was also observed following TPA treatment.

Cytoplasmic RNA was isolated at 2, 4, 8, and 24 h after TPA treatment and analyzed for c-*myc*-specific RNA (Fig. 4). TPA induces a large increase in c-*myc* mRNA within 2 h of treatment. However, unlike the case for GaMIg-treated cells, there was no drop in the mRNA level between 4 and 8 h of TPA treatment. RNA levels for c-*myc* remained relatively high during this period and were equivalent to the levels found in exponentially growing cells. A large decrease in the c-*myc* RNA level did occur between 8 and 24 h of TPA treatment. An analysis of cytoplasmic RNA isolated at early times following TPA treatment indicated that c-*myc* mRNA began to accumulate between 15 and 30 min and reached peak levels at 1 h of treatment (Fig. 4). TPA induction of c-*myc* was relatively specific, since no significant change in histone H3.2 RNA levels could be detected during this period (data not shown).

Since TPA has been shown to affect the transcription of the c-*myc* gene in other cell lines (16), nuclear run-on assays were performed on TPA-treated cells. Nuclei were isolated at 1, 2, 4, 8, and 24 h after TPA treatment and compared with untreated control cells (Fig. 4). TPA induced a large increase in the rate of c-*myc* gene transcription by 1 h. That rate remained relatively high through 8 h. After 24 h of treatment, the rate of c-*myc* gene transcription finally declined. These kinetics paralleled the changes in cytoplasmic mRNA levels (Fig. 4). Analysis of the earlier events indicates that the induction of c-*myc* gene transcription is rapid, occurring between 15 and 30 min. Similar results were obtained with the M13 sense-strand c-*myc* DNA on the filters (data not shown).

Conclusion. Changes in the rate of c-*myc* gene transcription and a transient stabilization of the labile c-*myc* mRNA are responsible for the rapid fluctuations observed in cytoplasmic c-*myc* mRNA levels in WEHI 231 cells. New protein synthesis is not required for the enhanced rate of transcription, since addition of cycloheximide, which effectively blocked more than 95% of the incorporation of [^{35}S]methionine, failed to prevent the increase (data not shown). The mechanism of stabilization of the c-*myc* mRNA is unknown but presumably involves transient inactivation of a selective ribonuclease activity.

The kinetics of the early changes in the levels of c-*myc* mRNA and gene transcription following treatment of WEHI 231 cells with TPA are similar to those of the early events following incubation with GaMIg. The action of phorbol esters in many systems has been found to be mediated through protein kinase C (25), an enzyme which has been implicated in the normal activation of quiescent cells, including resting B cells (6). Thus, while a role for this enzyme is suggested by these observations, the differences in the kinetics of decrease in c-*myc* mRNA levels and gene transcription with these two treatments imply involvement of other factors, in addition to protein kinase C, with the GaMIg incubation.

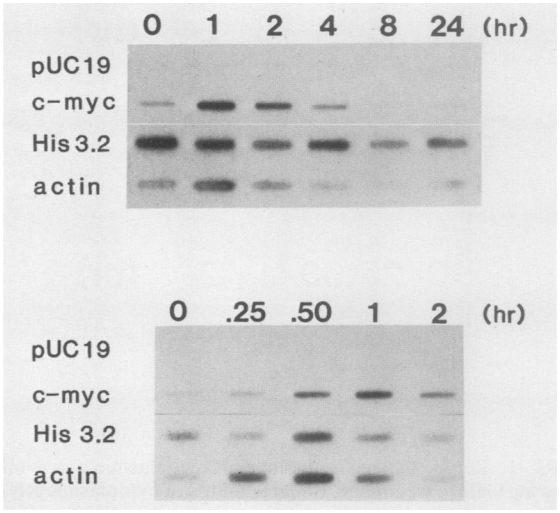

FIG. 3. Rapid changes in the rate of c-*myc* gene transcription as a result of GaMIg treatment. Nuclei were isolated by the method of Greenberg and Ziff (15) at the indicated times following anti-immunoglobulin antiserum treatment. Incorporation of [^{32}P]UTP per nucleus remained essentially constant over the time course. Nitrocellulose filters were prepared with 10 μg of DNA per slot (19). Hybridization reaction mixtures contained 2.5×10^6 cpm/ml of buffer [10 mM *N*-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (TES) (pH 7.4), 0.3 M NaCl, 10 mM EDTA (pH 8.0), 0.2% sodium dodecyl sulfate] containing the following additions: 50 μg of *Escherichia coli* tRNA per ml, 50 μg of denatured salmon sperm DNA per ml, 0.05% sodium pyrophosphate, and 2× Denhardt solution (11). Incubation of nuclei in the presence of 2 μg of α-amanitin per ml inhibited the synthesis of c-*myc* hybridizable transcripts. Cloned DNAs used were as follows: vector pUC19 as control, mouse c-*myc* cDNA, pM-c-*myc*-54 (31) (similar results were obtained if exon 1 was eliminated from the pM-c-*myc*-54 cDNA clone), mouse genomic fragment containing the histone H3.2 gene, pRAH3.2 (2), and rat β-actin cDNA clone containing the coding region capable of cross-actin species hybridization.

Interestingly, the reported sites of regulation of c-*myc* gene expression vary with the cell type under study and the specific treatment. Thus, while transcriptional control has been demonstrated in some cases, posttranscriptional regulation has been implicated in others. Greenberg and Ziff (15) demonstrated that changes in the rate of c-*myc* gene transcription are partially responsible for large changes in c-*myc* mRNA levels following addition of serum to quiescent murine BALB/c 3T3 fibroblasts (7, 20). The decrease in c-*myc* mRNA levels accompanying the monocyte or myeloid differentiation induced in human promyelocytic leukemia line HL60 by the addition of TPA or dimethyl sulfoxide, respectively, results from a decrease in the rate of gene transcription (16). In contrast, no concomitant decrease in c-*myc* gene transcription has been observed to explain the decline in the amount of c-*myc* mRNA during the terminal differentiation of F9 teratocarcinoma cells (10, 12) or the fluctuations in c-*myc* mRNA levels following addition of thrombin and insulin to quiescent Chinese hamster lung fibroblasts (4). A twofold decrease in the stability of c-*myc* mRNA explains in part the changes in c-*myc* mRNA levels seen after treatment of lymphoblastoid Daudi cells with interferon (9). The WEHI 231 cell line is unusual in that both transcriptional and posttranscriptional events have been demonstrated to play a role in regulating c-*myc* mRNA levels.

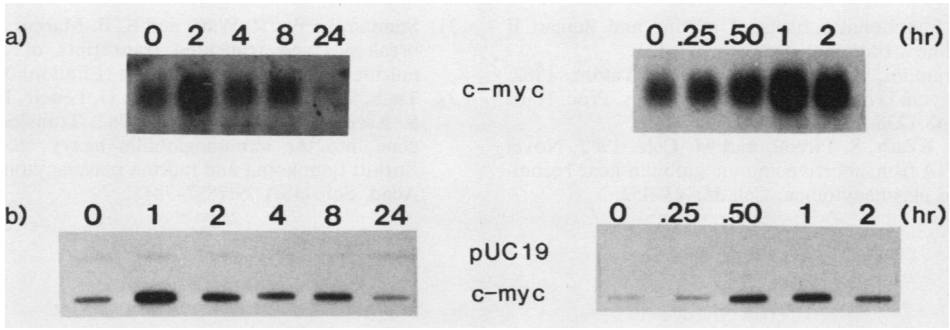

FIG. 4. Rapid changes in c-*myc* gene expression caused by treatment of WEHI 231 cells with TPA. (a) Cytoplasmic mRNA levels, assessed by Northern blotting as described for Fig. 1; (b) rate of gene transcription, assessed by run-on assays as described for Fig. 3.

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