Glucocorticoid Inhibition of c-myc, c-myb, and c-Ki-ras Expression in a Mouse Lymphoma Cell Line

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ABSTRACT

Glucocorticoid hormone treatment of certain T-cell-derived lymphomas and leukemias and of immature thymocytes results in cell death. Furthermore, glucocorticoid-mediated killing of S49 mouse lymphoma cells appears to involve the control of the cell cycle; i.e., S49 cells treated with glucocorticoids are arrested in G1 of the cell cycle when events controlling cell proliferation occur. The protooncogenes, c-myc, c-myb, and c-Ki-ras may be involved in cell cycle regulation and proliferation state in both normal and neoplastic cells. We report here that the steady state mRNA levels of c-myc, c-myb, and c-Ki-ras in S49 cells are dramatically and rapidly decreased after glucocorticoid treatment. Minimal expression is observed after 9 h, remaining at a constant low level at 11 h. Flow cytometry reveals no significant alteration in the cell cycle distribution of S49 cells up to 12 h after treatment. These findings suggest that glucocorticoids suppress the expression of these protooncogenes and that this may be the mechanism whereby glucocorticoids inhibit cell cycle progression in T-lymphoid cell lines.

INTRODUCTION

It has been known for many years that glucocorticoids exert dramatic effects on T-cell lymphomas, leukemias, and immature thymocytes (1–3). Glucocorticoid treatment of these cells causes a G1 arrest and eventual cell death (4, 5). Previous studies have examined the more general effects of the hormone on T-cell physiology, such as decreased glucose uptake (6), increased protein degradation (7), decreased thymidine incorporation into DNA (8), increased DNA fragmentation (9), and decreased ribosomal RNA synthesis (10), to name a few. Although interesting, it is difficult to determine whether the results obtained from these studies are caused directly by the hormone or are results of growth inhibition and the cell death process. Many of these physiological effects are only observed after lengthy exposure to the hormone. Since most of the physiological effects caused by glucocorticoids are due to changes in transcription, it seems probable that the genome is the primary site of hormone regulation. Indeed, not only do glucocorticoids stimulate gene transcription, but they also are capable of specifically inhibiting the transcription of certain genes. For example, the transcription of the α1-fetoprotein (11), ACTH (12, 13), and procollagen (14) genes is specifically inhibited by glucocorticoids in certain tissues.

Several reports on the killing of lymphoma cells have suggested that glucocorticoids influence the control of the cell cycle by inducing the arrest of cells in G0-G1 (4, 5). It is generally thought that in G0-G1 a cell is readied for growth and by mid-to-late G1, it becomes irreversibly committed to DNA synthesis and division. The expression of the cellular protooncogenes, c-myc, c-myb, and c-Ki-ras may be related to the proliferative state and cell cycle status of cells. For example, it has been suggested that c-myc and c-Ki-ras transcripts are present in augmented levels during G1 in actively proliferating fibroblasts, and T- and B-lymphocytes compared to their quiescent counterparts and that c-myc expression increases in G0-G1, while c-Ki-ras increases in mid-to-late G1 (15, 16). In chemically transformed fibroblasts, c-myc may be constitutively expressed while c-Ki-ras may be cell cycle-dependent (16). More recent studies suggest that c-myc levels may be constant throughout the cell cycle but are increased in actively proliferating cells (17, 18). The protooncogene, c-myb, has also been implicated in cellular proliferation or the differentiation state of cells. When human myeloblastic leukemia cells are induced to differentiate into nondividing cells, the levels of c-myb RNA decline followed by a decrease in DNA synthesis (19). All of these studies suggest that c-myc, c-myb, and c-Ki-ras expression may be necessary in allowing cells to progress through the cell cycle. One theory proposed for the mechanism of neoplastic transformation suggests that certain protooncogenes involved in cell cycle progression become inappropriately expressed at high levels, thereby resulting in uncontrolled growth or transformation. Continuous expression of these genes might then prevent a cell from entering the resting state. If this is the case, we surmise that glucocorticoids might inhibit the expression of c-myc, c-myb, and c-Ki-ras in S49 cells, thereby suppressing the ability of the cells to exit G1. The present study was carried out to investigate this possibility.

MATERIALS AND METHODS

Cell Culture. S49 cells were grown in DMEM (1 g/liter glucose) containing 10% heat-inactivated dialyzed fetal calf serum. Cultures were maintained in 2-liter spinner flasks at 37°C-10% CO2 in exponential growth (2–7 × 104 cells/ml). Cell viability was assessed by trypan blue exclusion. TA, a glucocorticoid analogue, was added to the spinner flasks at a final concentration of 1 μM. This glucocorticoid analogue was used because it is the most potent corticosteroid in the killing of S49 cells and in causing DNA fragmentation (9). Cells were harvested at various times after TA addition.

RNA Purification. Total cellular RNA was purified using the guanidinium thiocyanate method under sterile conditions (20). Cells were pelleted from medium by centrifugation at 10,000 × g for 15 min at 4°C and washed 3× in ice-cold Tris-saline (21). The pellets were then homogenized with a Polytron PT10 homogenizer (Brinkman Instruments) on setting 4 for 1 min in 4 M guanidine thiocyanate, 25 mM sodium citrate, 0.5% Sarkosyl, and 0.1 M β-mercaptoethanol, pH 7.0. One g of CsCl/2.5 ml vol was added to the homogenate. The mixture was then layered on a 1.2-ml cushion of 5.7 M CsCl in 0.1 M EDTA, pH 7.0 and centrifuged for 12–16 h in an SW50.1 swinging bucket rotor at 37,000 × gav. The RNA pellet was resuspended in 10 mM Tris-HCl-5 mM EDTA-0.5% sodium dodecyl sulfate-0.2 M NaCl, pH 7.2 and precipitated with ethanol. Poly(A)+-enriched RNA was selected by oligodeoxynucleotide cellulose chromatography using established methods (22). Total RNA was suspended in 0.01 M Tris buffer containing 0.4 M NaCl heated to 65°C for 5 min and applied to the column. The dropthrough was collected and reapplied 2× in the

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The abbreviations used are: DMEM, Dulbecco's modified Eagle's medium; TA, triamcinolone acetonide; IL-2, interleukin 2.
same manner. Poly(A)*-enriched RNA was eluted with 0.01 M Tris buffer.

Detection of RNA Transcripts. Poly(A)*-enriched RNA (5 μg/lane) was applied to 1.0% agarose gels containing 2.2 M formaldehyde and fractionated. RNA was transferred to nitrocellulose as described previously (23). The RNA bound to nitrocellulose was prehybridized overnight at 37°C in buffer containing 30% formamide-20 mm 4-(2-hydroxyethyl)1-piperazineethanesulfonic acid, pH 7.0, 5× Denhardt’s solution (1× Denhardt’s = 1% Ficoll-1% polyvinylpyrrolidone-1% bovine serum albumin), 3× standard saline citrate (1× standard saline citrate = 0.15 M NaCl-0.015 M sodium citrate, pH 7.0), denatured salmon sperm DNA (0.2 mg/ml), yeast RNA (0.1 mg/ml), 0.1% sodium dodecyl sulfate, and 3 mM EDTA. The nitrocellulose filters were then hybridized in freshly changed buffer containing nick-translated, 32P-labeled DNA probes for 72 h at 37°C. The DNA inserts used for hybridization were isolated by restriction enzyme digestion and agarose gel electrophoresis from their plasmids (with the exception of MMTV, which was not excised from the plasmid), provided by the following: Dr. Michael D. Cole (pm104BH, c-myc) (24); Dr. J. Michael Bishop (pvM2, v-myb) (25); Dr. Ronald W. Ellis (pHIIH3, c-Ki-ras) (26); Dr. Stuart A. Aaronson (1.2-kilobase PstI insert, v-sti) (27); Dr. Tatatsuugu Taniguchi (p3-16, IL-2) (28); Dr. Inder M. Verma (pHOS-1, v-fos) (29); Dr. Donald W. Cleveland (pA1, β-actin and pT1, α-tubulin) (30); Dr. John E. Majors (p4.2A, MMTV)* and Dr. Charles J. Sherr (0.5-kilobase PstI-PstI subclone of feline sarcoma virus, c-fes) (31).

Cell Cycle Analysis. Ten-ml aliquots were removed from spinner flasks containing untransformed cells or cells treated with 1 μM TA. The aliquots were pelleted at 1000 × g for 10 min and resuspended in 2 ml ice-cold DME (without serum). After an additional wash in DME, the cells were fixed in 70% ethanol at 4°C. The DNA was stained with chromomycin A₃ (32). Cell cycle analysis (percentages of G₀, S-phase, and G₂+M) was performed using a Becton-Dickinson FACS III flow cytometer. Approximately 8 × 10⁶ cells were analyzed for each profile.

Thymidine Incorporation into DNA. DNA synthesis was measured by pulse labeling 5 ml cell cultures for 30 min with [³H]thymidine, 2 μCi/ml (81.9 Ci/mmol; New England Nuclear). The cell suspensions were transferred to Whatman 2.4-cm GF/C glass fiber filters and vacuum was applied. The filters were washed twice with 10 ml each wash of ice-cold 10% trichloroacetic acid, dried in a vacuum oven, and the radioactivity determined by liquid scintillation counting at a counting efficiency of about 38%.

RESULTS

Cell Cycle Status and DNA Synthesis in Glucocorticoid-treated S49 Cells. S49 mouse lymphoma cells grow in suspension culture and have a doubling time of about 15-17 h in 10% fetal calf serum (8). In order to lower the glucocorticoid content of the serum, we dialyze it exhaustively. This results in a somewhat slower growth rate, with an average cell doubling time of about 24 h (data not shown). Exponentially growing cells treated with 1 μM TA are indistinguishable from untreated cells for the first 24 h of treatment with respect to growth rate and cell viability (trypan blue exclusion) (8). After this time lymphocytosis occurs (8). The main goal of this study was to determine if altered cellular proliferation and the previously observed G₂-G₁ arrest (4, 5) might be due to changes in protooncogene expression. Thus, it was imperative to determine if any lowering of protooncogene mRNA levels preceded or followed alterations in cell cycle distribution and DNA synthetic rate. If the former case were true, a direct effect of glucocorticoids on protooncogene expression would be possible, whereas the latter might indicate that changes in protooncogene mRNA levels are due to gross alterations in cell cycle status.

S49 cells were treated with 1 μM TA for up to 12 h, and the cell cycle status was determined by flow cytometry. The S49 cells in asynchronous culture had a large proportion (60-70%) of the cells in S phase (data not shown), as has also been noted previously by others (32). TA treatment of these cells for up to 12 h caused only a slight increase in the number of G₁ cells (Fig. 1). Earlier studies using undialyzed serum (doubling time = 15-17 h) demonstrated a virtual complete G₁ arrest 16-24 h after hormone treatment (4, 5, 32). It is probable that the very small increase in G₁ cells that we observed (3% at 12 h of treatment) is due to the large proportion of S-phase cells at the beginning of the treatment and the slower doubling time in dialyzed serum. This is substantiated by results obtained measuring the rate of DNA synthesis (Fig. 1). There was only a moderate effect of TA treatment on the incorporation of [³H]thymidine into DNA, with a plateau at about 75% of control levels between 6 and 12 h of hormone treatment. At 24 h after TA addition the level of DNA synthesis was 46% of control levels (data not shown). Thus, within the first 12 h of hormone treatment there was no dramatic lowering of DNA synthesis compared to untreated cells. As we had observed previously (8, 9), the number of viable (trypan blue-excluding) cells was the same in control and hormone-treated cultures at 24 h, and lymphocytosis commenced in TA-treated cultures after 24 h in the presence of hormone (data not shown). Since we wished to observe the rapid effects of glucocorticoids on gene expression which precede alterations in DNA synthesis or cell cycle status, we chose to use hormone-treatment times of less than 12 h.

Glucocorticoid Effects on Steady State Protooncogene RNA Levels. To investigate the effects of glucocorticoids on the control of the cell cycle in S49 cells, we first looked for the expression of those protooncogenes and growth factor genes already implicated in the regulation of cellular proliferation in other cell lines and tissues. S49 cell cultures in exponential growth (2-7 × 10⁶ cells/ml) were treated with TA at a final concentration of 1 μM. Total RNA was extracted from cells treated with TA for 3, 6, 9, and 11 h. Northern blots of poly(A)*-enriched RNA from each time point were hybridized to 32P-

* J. E. Majors, unpublished observations.
labeled DNA probes for c-myc, v-myb, c-Ki-ras, v-fos, c-fes, v-sis, and IL-2. Relatively high levels of c-myc-, v-myb-, and c-Ki-ras-related sequences were detected in poly(A)+-RNA from control cultures (untreated cells) (Fig. 2). However, after TA addition the expression of RNA homologous to c-myc, v-myb and c-Ki-ras was inhibited. The X-ray films were densitometrically scanned in order to determine the approximate amount of inhibition. The level of the 2.4-kilobase c-myc transcript decreased at 3 h after TA treatment to 24% of control levels, followed by a slow decline to 10 and 11% of control levels by 9 and 11 h, respectively. The c-myb transcript likewise decreased by 3 h after TA treatment to 27% of control levels, followed by an additional decline to 20% of control levels by 9 h. Expression of the 2.3-kilobase c-Ki-ras transcript decreased as early as 3 h after TA treatment to 40% of control levels, followed by a slow decrease to about 27% of control levels at both 9 and 11 h after TA treatment. Although not quantitated, a second less abundant 5.2-kilobase c-Ki-ras transcript appeared to decline at a rate similar to that of the 2.3-kilobase transcript. Transcripts homologous to v-fos, c-fes, v-sis, and IL-2 were not detectable in untreated controls or at any of the time points examined (data not shown).

Glucocorticoid Effects on Steady State Nononcogene RNA Levels. Despite the slight kinetic differences, a generalized decrease in c-myc, c-myb, and c-Ki-ras RNA was observed (Fig. 2). Thus, we examined the expression of three additional genes in the absence and presence of TA in an attempt to find a suitable internal control RNA which might be indicative of the general integrity of the cellular metabolic status; i.e., an overall decline in poly(A)+-enriched RNA levels in the cell after treatment with TA might suggest nonspecific changes in the cellular physiology, possibly due to the killing effects of the hormone, instead of a specific alteration in the expression of certain genes necessary for the cell's progression through the cell cycle. We chose the cytoskeletal genes β-actin and α-tubulin because of the ubiquitous presence of their protein products in cells. We also selected the mouse mammary tumor virus gene since glucocorticoids stimulate MMTV expression in several cell lines (33–36).

The expression of RNA homologous to both β-actin and α-tubulin as well as MMTV responded differently to TA treatment as compared to that observed for the protooncogenes. These results are shown in Fig. 3. The expression of a 1.7-kilobase α-tubulin transcript and the 2.2-kilobase β-actin transcript were not dramatically altered by TA treatment. Filters showing decreased levels of c-myc and c-myb transcripts upon hormone treatment were stripped and rehybridized with 32P-labeled β-actin and α-tubulin probes, respectively. No alteration in these control mRNA transcripts was noted (data not shown). Thus, the decreased protooncogene levels of TA treated cells is of a specific and not general nature. The expression of a 3.2-kilobase MMTV transcript increased after TA treatment to 193% of control levels at 3 h followed by a decrease to 10% of control levels at 6 h (Fig. 3). A 7.8- and a 1.6-kilobase transcript were also detected and although not quantitated they both increased at 3 h after hormone addition. This suggests that (at least at 3 h of TA treatment) the transcriptional machinery of the S49 cells is functional. Previous studies using a different assay detected no significant changes in MMTV RNA levels in S49 cells after glucocorticoid treatment (35). We have seen dramatic increases in MMTV RNA levels in these cells (see also below, Fig. 4B) and cannot yet explain the discrepancy with this previous study. The marked decrease of MMTV mRNA levels at the later time points is of substantial interest and needs further study.

It should be noted that the differential regulation of gene expression by glucocorticoids is dependent upon the overall physiology of the cell and the culture conditions. For example, in one experiment (data not shown) hormone treatment of S49 cells caused not only a lowering of protooncogene mRNA levels (similar to that seen in Fig. 2) but also a depression of β-actin and α-tubulin transcripts as well. However, in this experiment, the cell densities were between 0.9 and 1.1 × 10^6 cells/ml, as opposed to the cell concentration at which differential gene regulation was observed (0.2–0.7 × 10^6 cells/ml). We suspect that under conditions of high cell densities and depleted medium glucocorticoid treatment has an overall rapid deleterious effect on cell physiology. Thus, great care must be taken to use freshly seeded cells in log phase growth so that these extraneous effects on gene expression can be eliminated.
Rapid Time Course of the Glucocorticoid-mediated Inhibition of Protooncogene Expression. Clearly, the glucocorticoid-mediated inhibition of c-myc, c-myb, and c-Ki-ras expression within 3 h indicates a very rapid hormonal effect. Interestingly, the kinetics of inhibition are remarkably similar for all three transcripts. To determine if the decrease in expression of one protooncogene is a prerequisite for the inhibition of the others, earlier time points after glucocorticoid treatment were examined. Fig. 4A demonstrates that the mRNA levels for all three protooncogenes appeared to decline at about the same rate. The similarity in the decline of the c-myc, c-myb, and c-Ki-ras transcripts suggests two probable explanations. To begin with, the decrease in all three transcripts could be due to the overall effects of the cell death process. This seems unlikely since in this experiment MMTV expression was increased 10, 21, and 16-fold at 2, 3, and 4 h, respectively, after TA treatment (Fig. 4B). It should be noted that the kinetics of induction and fold induction of MMTV mRNA are similar to those found in other cells harboring the active MMTV provirus (reviewed in Ref. 36), although the decrease in MMTV transcript levels in S49 cells at longer times of hormone treatment has not been previously observed. This rapid decrease in MMTV transcript levels or perhaps slight variations in cellular physiology or culture state may be responsible for the variation in the absolute mRNA levels observed between separate experiments (e.g., those shown in Figs. 3 and 4B). In any event, this emphasizes the importance of performing the appropriate controls in every individual experiment, as was done here. An additional and more probable possibility for the coordinate decrease in all three protooncogene transcript levels is that all three protooncogenes act simultaneously in a concerted fashion to perpetuate cellular proliferation in S49 cells. Hence, the addition of the hormone could result in the coordinate decline in the expression of all three.

DISCUSSION

The results presented here show a rapid, specific, coordinate decrease in steady state protooncogene mRNA levels in glucocorticoid-treated T-lymphoma cells. These alterations in c-myc, c-myb, and c-Ki-ras expression clearly precede any significant changes in cell cycle status, growth rate, DNA synthetic rate, and cell viability. Since steroid hormones alter cellular physiology primarily via changes in gene expression, it is tempting to speculate that these alterations in protooncogene expression are due to a direct interaction of the glucocorticoid receptor complex with these genes.

Although the results obtained are intriguing, a number of important questions arise which must now be addressed. First, what is the molecular mechanism whereby glucocorticoids suppress protooncogene expression? Steroid hormones can both stimulate and inhibit RNA synthesis via altering the rates of transcription. In addition, postranscriptional effects of steroid hormones in stimulating and lowering gene expression, presumably due to a stabilization or destabilization of hormone-regulated mRNAs, species, have been shown (37-41). In reference to the regulation of c-myc gene expression, a wide variety of possible mechanisms have been proposed. For example, it has been claimed that interferon reduces c-myc expression by either suppressing gene transcription (42) or by decreasing mRNA stability (43). Furthermore, based upon the fact that cycloheximide causes a "superinduction" of c-myc transcript levels, it is possible that a labile repressor protein may inhibit c-myc gene transcription (15). Thus, it will be crucial to determine if the decreased steady state mRNA levels of c-myc, c-myb, and c-Ki-ras in glucocorticoid-treated S49 cells shown here are due to decreased RNA transcription, stability, and/or processing. Nuclear run-on and pulse-chase experiments are being initiated to address this problem.

The second important question is whether the observed G0-G1 arrest is specifically due to decreases in protooncogene mRNA levels. To address this, we have begun to analyze other cell lines whose growth rate and cell cycle status is affected by glucocorticoids. Preliminary studies with the human CEM-C7 acute lymphoblastic leukemia cell line (3) also show a rapid lowering in c-myc RNA levels followed by decreases in c-Ki-ras and c-myb RNA after TA treatment.5 (M. C. LaPointe and W. V. Vedeckis, unpublished). As with the S49 cell studies, the fact that CEM-C7 cells are killed by glucocorticoids complicates the interpretation of these data. However, c-myc RNA levels are also rapidly decreased in glucocorticoid-treated mouse L929 cells, and this precedes lowered c-Ki-ras RNA levels.6 (C. E. Reker and W. V. Vedeckis, unpublished). Since this fibroblastic line is growth inhibited but not killed by glucocorticoids, it seems plausible that c-myc at least may be directly controlled by glucocorticoids. Since the c-myc protein may act as an intracellular competence factor necessary for cells to proceed from G0-G1 to S phase (44), the glucocorticoid-mediated G0-G1 arrest observed in a number of cell lines may be due to decreased c-myc amounts.

A third important question is whether the alterations in protooncogene mRNA levels and the G0-G1 arrest are necessary for glucocorticoid-mediated T-cell lymphocyte lysis. The very rapid response of protooncogene mRNA levels to hormone treatment argue in favor of a role for this phenomenon in the cell death process. However, a genetic analysis of a different T-lymphoma cell line (SAK8) indicates the presence of a dominant "lysis" function or gene (reviewed in Ref. 45). Since the mechanism of action of this lysis gene is unknown, its relationship to alterations in protooncogene expression and the cell cycle arrest is unclear. Additionally, because c-myc and c-Ki-ras

\[ \text{Fig. 4. Rapid effects of glucocorticoid treatment on protooncogene and MMTV mRNA levels in S49 cells. S49 lymphoma cells were treated with 1 μM TA for the indicated times. Poly(A)+-enriched RNA was prepared and Northern blot analysis performed exactly as described in "Materials and Methods." A, X-ray films were scanned with a densitometer and the area under each curve was determined. Values are percentage of control (untreated) of protooncogene mRNA levels. B, A Northern blot was hybridized with a 32P-labeled MMTV probe and the X-ray film was scanned as described for A. The transcript level is expressed as the -fold increase, compared to control levels, in TA-treated cultures.} \]
mRNA levels are lowered in glucocorticoid-treated mouse L929 cells, but these cells are not killed, the inhibitory effect of glucocorticoids on protooncogene expression in T-cells is probably not sufficient for lymphocyteolysis. Obviously, a good deal of further study will be required to elucidate these relationships.

Finally, it will be important to determine if the modulation of protooncogene expression by steroid hormones is a common feature in cells whose growth rate is affected by steroid treatment. This will be of primary importance in the future study of steroid hormone-responsive tumors. In this regard, it has been shown (46) that the level of the c-Ha-ras transforming protein (with a molecular weight of 21,000) in an estrogen-responsive rat breast tumor is lowered by estrogen-removal (ovariectomy) and dibutyryl cyclic AMP treatment, and that the decrease in c-Ha-ras protein preceded tumor regression. Kasid et al. (47) showed that transfection of the v-Ha-ras gene into the estrogen-responsive human MCF-7 breast tumor cell line resulted in cells capable of forming tumors in a hormone-independent fashion. However, estrogen treatment did not stimulate the levels of endogenous myc, myb, Ha-ras, sis, erb B, or mht transcripts in MCF-7 cells. Thus, the role of protooncogene expression in estrogen-stimulated breast tumor cells is as yet unresolved. Another study has shown that 1,25-dihydroxyvitamin D3 causes a lowering (within 4 h) of c-myc mRNA in the human HL-60 promyelocytic leukemia cell line (48). This precedes by 8 h any phenotypic changes associated with differentiation of these cells into monocyte-like cells. Lastly, a hamster ductus deferens smooth muscle tumor cell line (DdT, MF-2) is arrested by glucocorticoids in G1 of the cell cycle, and this is accompanied by a decrease in the sis (homologous to the β chain of platelet-derived growth factor) mRNA levels (49, 50). Most importantly, glucocorticoid-arrested cells can be stimulated to divide by the addition of exogenous platelet-derived growth factor (49). This suggests that glucocorticoids can inhibit the synthesis of a growth factor involved in the autocrine stimulation of cell division. A similar conclusion has been reached using a glucocorticoid-inhibited tumor cell line derived from the Dunning rat prostate adenocarcinoma (51). Future studies on estrogen-, androgen-, vitamin D-, and glucocorticoid-responsive neoplasias will elucidate the possible modulation of cellular proliferation by steroid hormones via the regulation of responsive neoplasias.

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REFERENCES


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