Notice of Retraction

Re: Henschler R, Brennscheidt U, Mertelsmann R, and Herrmann F (1991) Induction of c-jun expression in the myeloid leukemia cell line KG-1 by 1-β-D-arabinofuranosylcytosine. *Mol Pharmacol* 39:171–176

The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), the central, self-governing research funding organization in Germany, has notified *Molecular Pharmacology* that the above article by Henschler et al. (1991) contains falsified information. An interinstitutional task force organized by the DFG investigated falsification allegations against Prof. Friedhelm Herrmann and Marion Brach. Prof. Herrmann is the corresponding author of the above article. The task force determined that the above article was falsified. *Molecular Pharmacology* was officially notified of this in a letter from Dr. Reinhard Grunwald dated October 30, 2006.

The article was retracted on November 14, 2006.

Board of Publications Trustees
ASPET

0026-895X/91/020171-06$03.00/0

MOLECULAR PHARMACOLOGY, 39:171-176

Induction of c-*jun* Expression in the Myeloid Leukemia Cell Line KG-1 by 1-β-D-Arabinofuranosylcytosine

R. HENSCHLER, U. BRENNSCHEIDT, R. MERTELSMANN, and F. HERRMANN

Department of Hematology and Oncology, University of Freiburg Medical Center, Freiburg, Federal Republic of Germany

Received May 17, 1990; Accepted November 7, 1990

SUMMARY

c-Jun/AP-1 is a transcription factor commonly induced in mammalian cells by serum, phorbol compounds, or peptide growth factors. We show that c-Jun/AP-1 is inducible as well as coordinately regulated, in the human acute myelogenous leukemia cell line KG-1, by the cytostatic drug 1-β-D-arabinofuranosylcytosine (Ara-C). Concomitantly with Ara-C treatment, growth inhibition and loss of clonogenic survival of KG-1 cells were observed. Whereas KG-1 cells displayed only barely detectable amounts of c-*jun* transcripts when cultured in the presence of serum, Ara-C at concentrations of 1 to 50 μM induced c-*jun* transcripts in a dose-dependent fashion. Time course studies showed that 10 μM Ara-C induced c-*jun* transcripts 6 hr after initiation of culture. Induction of c-*jun* mRNA was independent of *de novo* protein synthesis, because the protein synthesis inhibitor cycloheximide failed to alter Ara-C-induced c-*jun* mRNA accumulation. Furthermore, cycloheximide did not induce c-*jun* transcripts, ruling out the possibility of posttranscriptional stabilization of c-*jun* mRNA by labile proteins, as has been previously reported for a variety of serum-inducible protooncogenes and early response genes. Moreover, nuclear run-on analysis disclosed that c-*jun* induction by Ara-C in KG-1 cells took place at a transcriptional level. Taken together, these findings indicate that c-*jun* mRNA, unlike its rapid (within minutes) induction by serum in fibroblasts, is induced by Ara-C in KG-1 cells following a much more prolonged time course and is regulated essentially at a transcriptional level.

The c-*jun* protooncogene is the normal cellular homolog of the avian sarcoma virus 17 transforming gene (1). The 39,000 protein product of c-*jun* is the major constitutive element of the mammalian transcription factor AP-1 (2, 3). c-Jun is structurally similar to GCN 4, a DNA-binding protein involved in yeast gene regulation (4). GCN 4 and AP-1 bind to a specific DNA *cis*-element, the TPA-responsive element, containing the TGACTCA motif (5). This motif has been found to be part of the 5′ flanking sequences of an increasing number of cell growth-associated genes. c-*jun* expression is rapidly inducible in fibroblasts by serum and phorbol esters (6). Also, a number of polypeptide growth factors have been shown to either enhance or induce c-*jun* expression in various cell types, such as epidermal growth factor (7), transforming growth factors -α (8) and -β (9), and nerve growth factor (10). In endothelial cells, the antimitogenic action of tumor necrosis factor-α was associated with elevations in c-*jun*/AP-1 (11), thus confirming that c-*jun*/AP-1 induction is not exclusively related to mitogenic/proliferative cellular events.

Ara-C is an S phase-specific cytotoxic drug extensively used in the treatment of various hematologic malignancies, including acute myelogenous leukemia and the myelodysplastic syndrome. Its mechanism of action as a nucleoside analog is to cause incorporation of Ara-CTP instead of dCTP into DNA during DNA synthesis and to terminate chain elongation (12). Apart from its cytostatic potential, Ara-C is also known to exert antiviral effects (13). Furthermore, Ara-C treatment is associated with differentiation of various human hematopoietic cell lines (14, 15). During induction of differentiation of HL-60 or U 937 human myeloid cell lines, alterations in expression of the protooncogenes c-*myc* and c-*fos* have been observed. Previous experiments of our own have shown that Ara-C treatment resulted in a transient increase of c-*fos* transcripts in KG-1 cells (12). Because heterodimer formation between c-Fos and c-Jun proteins has been reported to result in complexes with DNA binding affinities exceeding those of Jun-Jun homodimers by far (16), we thought to address in this study the question of whether Ara-C was also capable of inducing c-*jun* transcripts in KG-1 cells. A more recent study showed that c-*jun* mRNA levels increased during differentiation of HL-60, U 937, and THP-1 induced by the phorbol ester TPA, indicating a role of c-*jun* in monocytic differentiation (17). Transcriptional as well as posttranscriptional mechanisms were shown to govern protein kinase C-mediated c-*jun* mRNA accumulation in these cells. Little is known, however, about the expression of c-*jun* associated with Ara-C treatment and the mechanisms of c-*jun* gene regulation by Ara-C in myeloid cells.

ABBREVIATIONS: TPA, tetradecanoylphorbol-13-acetate; Ara-C, 1-β-D-arabinofuranosylcytosine; CHX, cycloheximide; kb, kilobase; MOPS, *N*-morpholinopropanesulfonic acid; SSC, standard saline citrate.

Materials and Methods

Cell culture and clonogenic assay. KG-1 and KG-1a cells (kindly provided by Dr. H. P. Koeffler, University of California, Los Angeles, CA) were cultured in RPMI 1640 medium (GIBCO/BRL Laboratories, Paisley, UK), supplemented with 10% low-endotoxin fetal calf serum (Hazelton Laboratories, Vienna, UT), L-glutamine, and penicillin/streptomycin (Sigma Chemicals, Munich, FRG), at densities of 1–5 × 10^5 cells/ml. Ara-C, Actinomycin D, CHX, and the phorbol ester TPA (all from Sigma) were diluted in RPMI 1640 before use. After the incubation periods (2–24 hr), cells were collected by centrifugation and washed. For clonogenic assays, cells that were previously exposed to Ara-C for 1–24 hr were plated, after several washings, at 1 × 10^3/well in 0.3% agarose (Difco Laboratories, Detroit, MI), on top of an underlayer consisting of 0.5% agarose in RPMI/fetal calf serum, in 24-well plates. After the culture period, agar overlayers were removed from underlayers by agitation, dried onto glass slides, fixed in methanol, and stained with acidic hematoxylin (Sigma). Colonies with >20 cells were enumerated.

RNA preparation, Northern blot analysis, cDNA probes, and nuclear run-on transcription assay. Cells were lysed with 4 M guanidinium isothiocyanate (Sigma) and extracted by the cesium chloride method (18). Samples were fractionated by electrophoresis through a 1% agarose gel in 0.02 M MOPS (Serva, Heidelberg, FRG), pH 7.0, 0.66 M formaldehyde, transferred to synthetic membranes (Schleicher and Schuell, Dassel, FRG), and hybridized to a minimum of 10^6 cpm/ml ^{32}P-labeled cDNA probes. cDNA probes (50 ng) were labeled with [^{32}P]dCTP (3000 Ci/mmol; Amersham, Braunschweig, FRG), using the hexanucleotide primer technique (19). The filters were washed to a final stringency of 0.1× SSC (1× SSC is 0.15 M sodium chloride, 0.015 M sodium citrate, pH 7.0) at 65° and exposed to Kodak X-Omat films with intensifying screens for 1–3 days. For nuclear run-on transcription assays, cells (10^8) were lysed in RSB (10 mM Tris·HCl, 5 mM KCl, 3 mM $MgCl_2$) containing 0.5% Nonidet-P 40 (Sigma) and were washed once in ice-cold phosphate-buffered saline. Nuclei were incubated at 26° in 15% glycerol, 70 mM KCl, 2.5 mM $MgCl_2$, 10 mM EDTA, 4 mM levels each of ATP, CTP, and GTP, 2 mM UTP, 0.5 mM dithiothreitol, 60 units/ml RNasin (Boehringer Mannheim, Mannheim, FRG), in the presence of 100 μCi of [^{32}P]UTP (3000 Ci/mmol; Amersham), for 30 min. The mixture was digested with DNase 1 and proteinase K, extracted with trichloroacetic acid and phenol/chloroform, and precipitated in 70% ethanol before hybridization of 5 × 10^6 cpm/ml of hybridization buffer [50% formamide, 2× SSC, 1% sodium dodecyl sulfate, 5× Denhardt's solution (1× Denhardt's is 0.02% Ficoll, 0.02% bovine serum albumin (fraction V; Sigma), 0.02% polyvinylpyrrolidone), 50 μg/ml tRNA]. Filters contained 10 μg each of linearized plasmids immobilized on nitrocellulose (Schleicher and Schuell) after blotting with a slot-blot apparatus (Schleicher and Schuell). After hybridization at 42° for 3 days, filters were rinsed in 2× SSC at 55°, 2× SSC containing 10 μg/ml RNase A at 37°, and finally 0.5× SSC at 55°, for 30 min each time, and were exposed to Kodak X-Omat films for 10 days. Plasmids and cDNA probes used were the 0.8-kb *Bam*HI-*Pst*I chicken α-actin fragment in pBR 322 (20), the 1.2-kb *Eco*RI-*Bam*HI fragment of human c-*jun* in p Bluescript SK (3), and the 414-base pair *Pst*I-*Pst*I fragment of human c-*myc* in pHSRI (21). All experiments were repeated three times. A representative result is shown for each experiment.

Results

Whereas c-*jun* expression was barely detectable in untreated cultures of KG-1 cells (10^5 cells/ml), exposure to 1 μM Ara-C for 6 hr resulted in induction of 2.7-kb c-*jun* transcripts (Fig. 1). Ara-C at 10 and 50 μM further increased c-*jun* transcript levels. A time course study with 10 μM Ara-C revealed that 15 μg of KG-1 total cytoplasmic RNA contained c-*jun* transcripts, with a peak observed at 6 hr. c-*jun* mRNA returned to almost

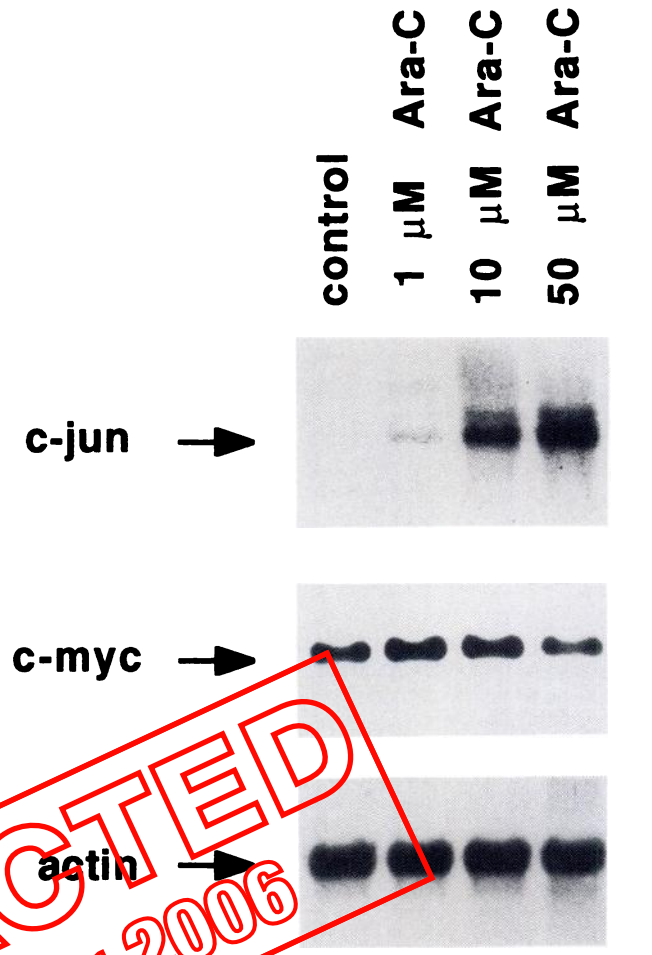

Fig. 1. Induction of c-*jun* mRNA expression in KG-1 cells by various concentrations of Ara-C. KG-1 cells were treated with 1, 10, or 50 μM Ara-C for 6 hr and harvested thereafter. Total cytoplasmic RNA was isolated, and 15 μg of RNA were sequentially hybridized to specific cDNA probes for c-*jun*, c-*myc*, and α-actin.

starting levels within 24 hr (Fig. 2). In contrast, α-actin mRNA levels were unaffected by Ara-C-treatment at all time points and concentrations investigated (Figs. 1–5). Exposure of KG-1 cells to concentrations of 1–50 μM Ara-C resulted in a slight decrease of expression of c-*myc* transcripts (Figs. 1 and 2). When cells were cultured in the presence of the phorbol ester TPA (10^{-9} M), c-*jun* transcripts became detectable after 2 hr of treatment and were still at a relatively high level at 24 hr (Fig. 3).

Ara-C-mediated induction of c-*jun* mRNA was not dependent on *de novo* protein synthesis, inasmuch as comparable signal intensities of c-*jun* transcripts were obtained in both the presence and absence of the protein synthesis inhibitor CHX (Fig. 4). Moreover, CHX was not able to induce c-*jun* transcript levels by itself, ruling out posttranscriptional regulation of c-*jun* expression by mRNA-stabilizing proteins (Fig. 4). Complete blockade of protein synthesis in these experiments was confirmed by the lack of [^{14}C]leucine incorporation into the cells over a 6-hr period (data not shown). When cells were treated with TPA (10^{-9} M), exposure to CHX resulted in superinduction of c-*jun* transcripts (Fig. 3), suggesting a considerable impact of posttranscriptional mechanisms on TPA-induced c-*jun* mRNA expression. This was assayed by densitometric scanning of Northern blot signals and normalization to actin transcript

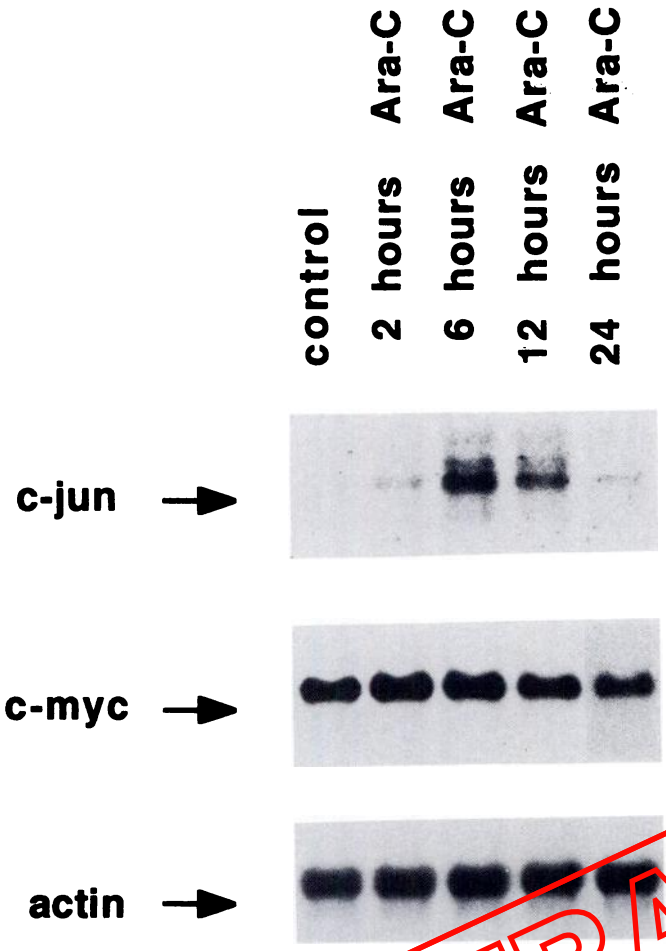

Fig. 2. Induction of c-*jun* mRNA in KG-1 cells after different times of exposure to Ara-C. Fifteen micrograms of total RNA were isolated from KG-1 cells treated with 10 μM Ara-C for the indicated periods and were hybridized to c-*jun*, c-*myc*, and α-actin cDNA probes.

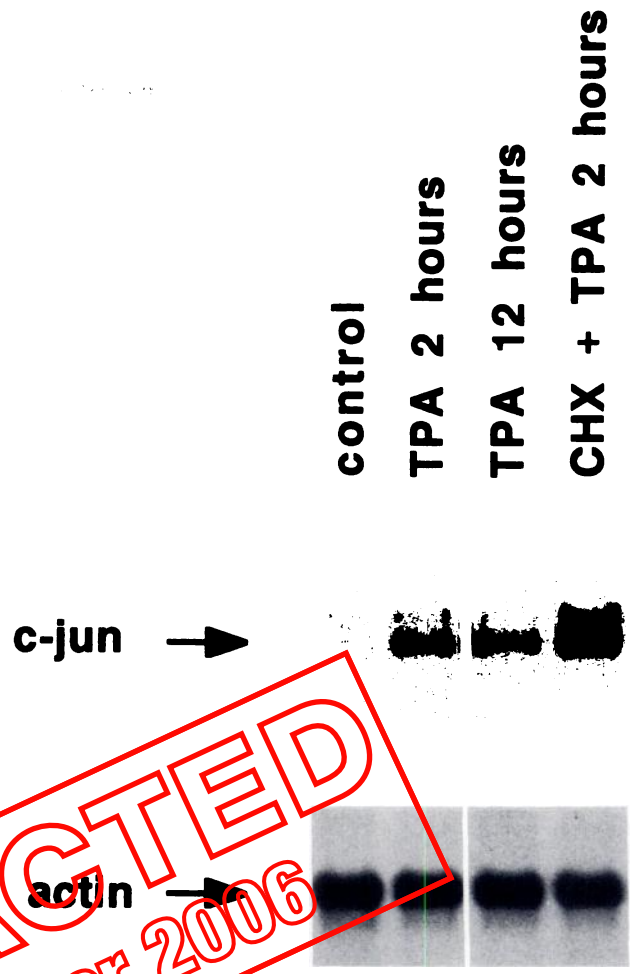

Fig. 3. Induction of c-*jun* mRNA in KG-1 cells by the phorbol ester TPA. KG-1 cells were exposed to 10^{-9} M TPA for 2 or 24 hr or were pretreated with 50 μg/ml CHX for 10 min before TPA was added to a final concentration of 10^{-9} M. Fifteen micrograms of total cellular RNA were hybridized to c-*jun* or α-actin cDNA probes. Autoradiographic signals were analyzed by laser densitometry.

levels. c-*myc* transcript levels remained constant in the experiments shown in Figs. 3 and 4 (not shown). Densitometric scanning of signal levels from Actinomycin D studies showed that c-*jun* transcripts induced by treatment with 10 μM Ara-C for 6 hr had a half-life of approximately 1 hr, as measured by densitometric scanning (Fig. 5). c-*myc* mRNA half-life was comparable to that of c-*jun* mRNA (not shown). Nuclear run-on assays confirmed that induction of c-*jun* transcripts by Ara-C is regulated at the transcriptional level (Fig. 6).

Although cell viability, as assessed by trypan blue dye exclusion, was not significantly affected by Ara-C treatment (1–50 μM, 24 hr) of KG-1 cells (data not shown), clonogenic survival of KG-1 cells cultured in agar for 7 days decreased dose dependently upon exposure to Ara-C for 1–24 hr (Table 1), indicating that Ara-C did not confer immediate toxicity to KG-1 cells at the concentrations used. Treatment of the differentiation-defective subclone of KG-1, KG-1a, with 1–50 μM Ara-C also revealed a clear induction of c-*jun* transcripts (Fig. 7), supporting the notion that Ara-C-mediated c-*jun* induction is not associated with differentiation of KG-1 cells.

Discussion

The protooncogene c-*jun* was initially defined as a member of the immediate early gene family and was thought to play a key role in the activation of fibroblasts by serum, phorbol esters, and growth factors (6). Its protein product, the mammalian transcription factor AP-1, is known to bind to the TPA-responsive element that regulates a number of cell growth-associated genes. Its homology to GCN 4, a yeast homolog of AP-1, suggests that this structure was highly conserved during the evolution of heterotrophic organisms and that it plays a role as an essential component in the transcriptional control of genes encoding vital cell functions.

In our studies, Ara-C treatment of KG-1 cells resulted in a dose-dependent induction of c-*jun* transcripts, which, unlike their rapid (within minutes) induction by serum or TPA in fibroblasts, followed a much more prolonged time course. Furthermore, the protein synthesis inhibitor CHX did not enhance Ara-C-mediated c-*jun* mRNA expression. CHX was also unable to induce c-*jun* transcripts by itself. Therefore, short lived mRNA-stabilizing proteins, reported to exert major effects on the increase in mRNA levels of a variety of other protooncogenes, as well as that of serum-induced c-*jun* (6, 22, 23), appear to have no role in Ara-C-mediated induction of c-*jun*. Hence, in contrast to serum-induced c-*jun* in fibroblasts, Ara-C-induced c-*jun* in KG-1 cells was regulated at a transcriptional level. Nuclear run-on assays showed that, whereas the c-*jun*

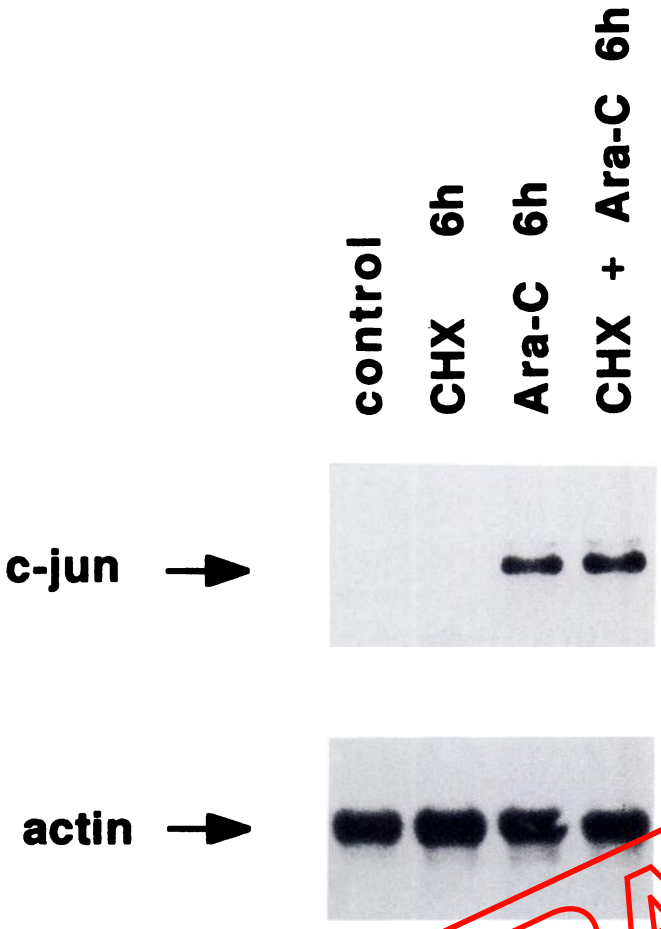

Fig. 4. Effect of the protein synthesis inhibitor CHX on c-*jun* mRNA expression in KG-1 cells induced by Ara-C. Total cellular RNA was obtained from untreated KG-1 cells (*control*) or cells treated with either 10 μM Ara-C or 50 μg/ml CHX alone for 6 hr or with both for the same period. mRNA for c-*jun* and α-actin genes was detected by hybridization to their respective cDNA probes. As in Fig. 3, autoradiographic signals were analyzed by laser densitometry.

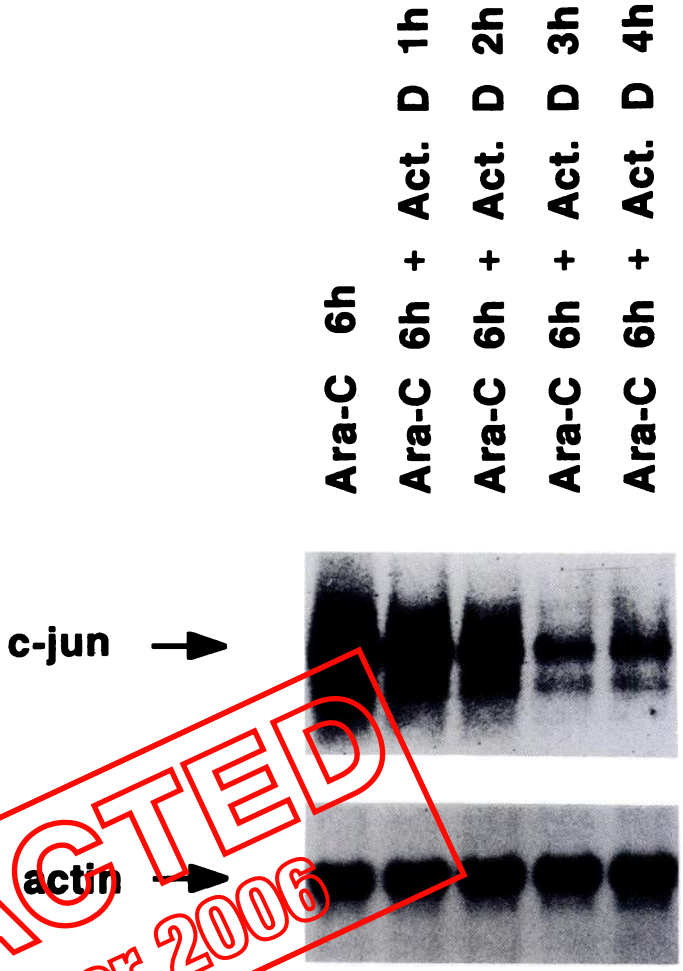

Fig. 5. Northern blot analysis of c-*jun* mRNA half-life after induction with Ara-C. KG-1 cells were treated with 10 μM Ara-C for 6 hr before Actinomycin D (*Act. D*) (5 μg/ml) was added for the indicated intervals. Twenty micrograms of total cellular RNA were hybridized to c-*jun* and α-actin cDNA probes. Intensities of autoradiographic exposures were analyzed by laser densitometry.

gene was transcriptionally inactive in untreated cells, treatment of KG-1 cells with 10 μM Ara-C for 3 hr resulted in a more than 20-fold enhanced rate of c-*jun* transcription. In another set of experiments Actinomycin D was added to the cultures for various durations after induction of *jun* expression by Ara-C, to study c-*jun* mRNA stability. The decrease in signal intensities, as determined by densitometric scanning, indicated that the half-life of c-*jun* mRNA was approximately 1 hr.

The 3′ untranslated region of c-*jun* mRNA contains AU-rich sequences, which are thought to regulate mRNA instability by allowing short lived RNA-binding proteins to specifically control cleavage and subsequent degradation of mRNAs coding for protooncogenes and growth factors (24, 25). However, unlike it was demonstrated for the regulation of gene expression of c-*jun* as well as c-*fms* and c-*fos* protooncogenes during mitogenic stimulation (6) and monocytic differentiation (17, 22, 23), Ara-C-mediated induction of c-*jun* expression in KG-1 cells was unaffected by posttranscriptional regulative mechanisms.

Viability of cells was greater than 90% at all time points and concentrations of Ara-C investigated, demonstrating that Ara-C did not confer immediate toxicity to the cells. Clonogenic survival was severely impaired over a 6-day culture period when Ara-C doses exceeded 1 μM. However, c-*jun* was also inducible following treatment of the differentiation-defective subclone of KG-1, KG-1a. This gives an indication that c-*jun* is not likely to play a role in Ara-C-mediated induction of differentiation in KG-1 cells. A discrepancy is observed between the kinetics of induction of c-*jun* gene by TPA and that by Ara-C. Moreover, superinduction in the presence of CHX was only seen in TPA-treated cells. Apart from the assumption that Ara-C-mediated cell signaling and transcriptional control are not expected to be mediated by protein kinase C (as is the case with TPA), different regulative mechanisms on the c-*jun* gene promoter/enhancer level may also be expected.

The nuclear protein c-Fos is known to enhance the DNA-binding affinity of Jun protein by the formation of a Jun-Fos dimer via the leucine zipper motif (26, 27). Jun-Fos dimers exhibit by far higher DNA-binding affinities than Jun-Jun homodimers (16). We have previously observed induction of c-*fos* transcripts in KG-1 cells by Ara-C (12). Because Ara-C-induced c-*fos* expression followed a very similar dose dependence and time course, compared with that of c-*jun* in our present experiments, it is inferred that the induction of both c-*fos* and c-*jun* transcripts may be the prerequisite for a coordinate interplay of both protooncogenes to regulate gene expres-

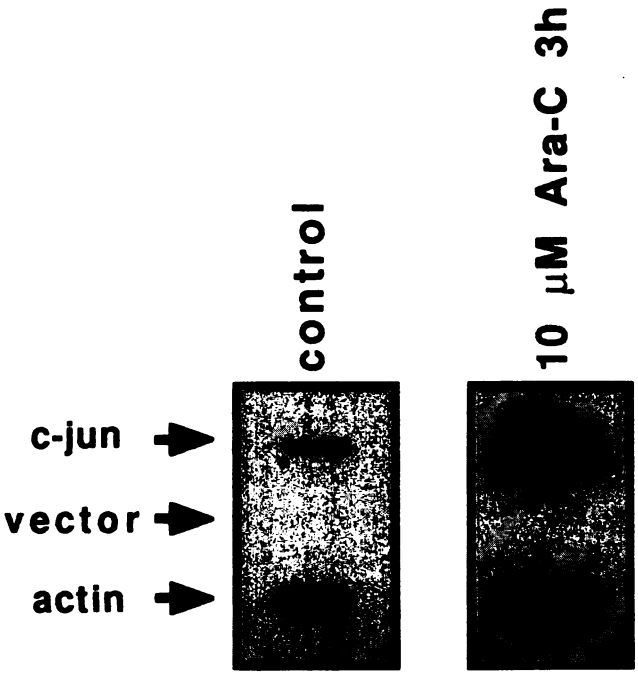

Fig. 6. Nuclear run-on analysis of c-*jun* gene transcription in KG-1 cells. KG-1 cells (10^8) were exposed to medium only (*control*) or to 10 μM Ara-C for 3 hr, and nuclei were assayed for transcriptional activity of the α-actin, c-*jun*, and vector (pB KS) cDNA.

TABLE 1

Clonogenic survival of KG-1 cells upon exposure to Ara-C

KG-1 cells (10^3/well) were exposed for the indicated times to Ara-C (1 and 10 μM) or medium only in liquid cultures, washed three times, and incorporated in agar cultures (37°, 5% CO_2 in a humidified atmosphere in air). After 7 days, clones of KG-1 cells with >20 cells were enumerated. Numbers of clones are expressed as means ± standard errors of triplicate cultures of two independent experiments.

Exposure time	No. of clones		
	Medium only	1 μM Ara-C	10 μM Ara-C
0	208 ± 18	209 ± 19	208 ± 19
1	207 ± 22	166 ± 19	165 ± 18
2	206 ± 20	133 ± 24	123 ± 19
6	199 ± 21	101 ± 18	83 ± 11
12	193 ± 17	69 ± 13	49 ± 8
24	191 ± 18	36 ± 7	22 ± 4

sion through binding to AP-1 consensus DNA elements on a class of Ara-C-inducible genes.

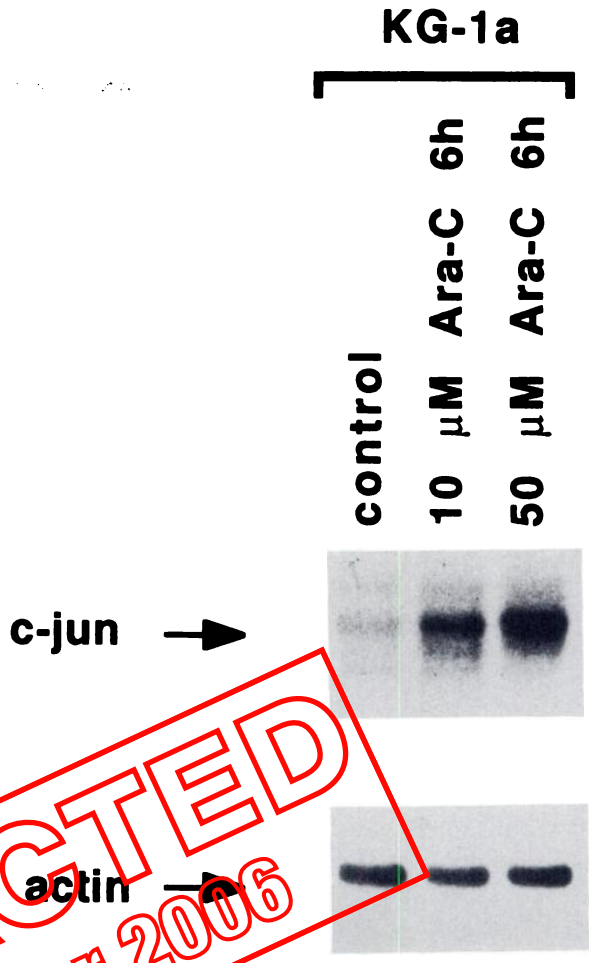

Fig. 7. Northern blot analysis of c-*jun* mRNA induction by Ara-C in KG-1a cells. KG-1a cells were treated with either medium alone (*control*) or 10 or 50 μM Ara-C for 6 hr. Fifteen micrograms of total cellular RNA were hybridized to c-*jun* and α-actin cDNA probes.

References

1. Maki, Y., T. J. Bos, C. Davis, M. Starbuck, and P. Vogt. Avian sarcoma virus 17 carries the *jun* oncogene. *Proc. Natl. Acad. Sci. USA* **84**:2848–2852 (1987).
2. Bohmann, D., T. J. Bos, A. Admon, T. Nishimura, P. K. Vogt, and R. Tijan. Human protooncogene c-*jun* encodes a DNA binding protein with structural and functional properties of transcription factor AP-1. *Science (Washington D. C.)* **238**:1386–1392 (1987).
3. Angel, P., E. A. Allegretto, S. T. Okino, K. Hatton, W. J. Boyle, T. Hunter, and M. Karin. Oncogene *jun* encodes a sequence-specific transactivator similar to AP-1. *Nature (Lond.)* **332**:166–171 (1988).
4. Vogt, P. K., T. J. Bos, and R. F. Doolittle. Homology between the DNA-binding domain of the GCN 4 regulatory protein of yeast and the carboxy-terminal region of a protein coded for by the oncogene *jun*. *Proc. Natl. Acad. Sci. USA* **84**:3316–3319 (1987).
5. Mitchell, P. J., and R. Tijan. Transcriptional regulation in mammalian cells by sequence-specific DNA binding proteins. *Science (Washington D. C.)* **245**:371–378 (1989).
6. Ryder, K., and D. Nathans. Induction of protooncogene c-*jun* by serum growth factors. *Proc. Natl. Acad. Sci. USA* **85**:8464–8467 (1988).
7. Quantin, B., and R. Breathnach. Epidermal growth factor stimulates transcription of the c-*jun* proto-oncogene in rat fibroblasts. *Nature (Lond.)* **334**:538–539 (1989).
8. Brenner, D. A., K. S. Koch, and H. L. Leffert. Transforming growth factor-*alpha* stimulates proto-oncogene c-*jun* expression and a mitogenic program in primary cultures of adult rat hepatocytes. *DNA* **8**:279–285 (1989).
9. Pertovaara, L., L. Sistonen, T. J. Bos, P. K. Vogt, J. Keski-Oja, and K. Alitalo. Enhanced *jun* gene expression is an early genomic response to transforming growth factor *beta* stimulation. *Mol. Cell. Biol.* **9**:1255–1262 (1989).
10. Wu, B., E. J. B. Fodor, R. H. Edwards, and W. J. Rutter. Nerve growth factor induces the proto-oncogene c-*jun* in PC-12 cells. *J. Biol. Chem.* **264**:9000–9003 (1989).
11. Dixit, V. M., R. M. Marks, V. Sarma, and E. V. Prochownik. Antimitogenic action of TNF is associated with increased AP-1/*jun* in endothelial cells. *J. Biol. Chem.* **264**:16905–16909 (1989).
12. Brach, M., H. Klein, E. Platzer, R. Mertelsmann, and F. Herrmann. Effect of interleukin-3 on cytosine arabinoside-mediated cytotoxicity of leukemic myeloblasts. *Exp. Hematol.* **18**:748–753 (1990).
13. Chien, L. T., F. M. Schabel, and C. A. Alford. Arabinosyl nucleosides and nucleotides: preliminary report, in *Selective Inhibitors of Viral Functions* (W. A. Carter, ed.). CRC Press Inc., Cleveland, OH, 227–258 (1973).
14. Mitchell, T., E. Sariban, and D. Kufe. Effects of 1-β-D-arabinosylfuranylcytosine on protooncogene expression in human U-937 cells. *Mol. Pharmacol.* **30**:398–402 (1986).
15. Pinto, A., V. Attadia, R. Rosati, G. Colletta, R. Cimino, and A. Colombatti. Differentiation of human leukemic cell lines and fresh leukemia cells by low-dose Ara-C: monitoring by expression of c-*myc* and c-*fos* oncogenes. *Med. Oncol. Tumor Pharmacother.* **5**:91–97 (1988).
16. Halazonetis, T. D., K. Georgopoulos, M. E. Greenberg, and P. Leder. C-Jun dimerizes with itself and with c-Fos, forming complexes of different DNA binding affinities. *Cell* **55**:917–924 (1988).
17. Sherman, M. L., R. M. Stone, R. Datta, S. H. Bernstein, and D. W. Kufe. Transcriptional and posttranscriptional regulation of c-*jun* expression during monocytic differentiation of human myeloid leukemic cells. *J. Biol. Chem.* **265**:3320–3323 (1990).
18. Chirgwin, J. M., A. E. Przybyla, R. J. McDonald, and W. Rutter. Isolation of

biologically active ribonucleic acid from sources enriched in ribonuclease. *Biochemistry* **18**:5294–5299 (1979).
19. Feinberg, A. P., and B. Vogelstein. A technique for radiolabeling DNA restriction endonuclease fragments to high specific activity. *Anal. Biochem.* **132**:6–13 (1983).
20. Schwartz, R. J., J. A. Haron, K. N. Rothblum, and A. Dugaiczyk. Regulation of muscle differentiation: cloning of sequences from *alpha*-actin messenger ribonucleic acid. *Biochemistry* **19**:5883–5890 (1980).
21. Alitalo, K., M. Schwab, C. C. Lin, H. E. Varmus, and J. M. Bishop. Homogeneously staining chromosomal regions contain amplified copies of abundantly expressed cellular oncogene (c-*myc*) in malignant neuroendocrine cells from a human colon carcinoma. *Proc. Natl. Acad. Sci. USA* **80**:1707–1711 (1983).
22. Sariban, E., R. Luebbers, and D. Kufe. Transcriptional and posttranscriptional control of c-*fos* gene expression in human monocytes. *Mol. Cell. Biol.* **8**:340–346 (1988).
23. Weber, B., J. Horiguchi, R. Luebbers, M. Sherman, and D. Kufe. Posttranscriptional stabilization of c-*fms* mRNA by a labile protein during human monocytic differentiation. *Mol. Cell. Biol.* **9**:769–775 (1989).
24. Shaw, G., and R. Kamen. A conserved AU sequence from the 3′ untranslated region of GM-CSF mRNA mediates selective mRNA degradation. *Cell* **46**:659–667 (1986).
25. Wilson, T., and R. Treisman. Removal of poly(A) and consequent degradation of c-fos mRNA facilitated by 3′ AU-sequences. *Nature (Lond.)* **336**:396–399 (1988).
26. Curran, T., and R. B. Franza, Jr. Fos and Jun: the AP-1 connection. *Cell* **55**:395–397 (1988).
27. Kouzarides, T., and E. Ziff. Leucine zippers of fos, jun and GCN4 dictate dimerization specificity and thereby control DNA binding. *Nature (Lond.)* **340**:568–571 (1989).

Send reprint requests to: F. Herrmann, Department of Hematology and Oncology, University of Freiburg Medical Center, Hugstetter Strasse 55, D-7800 Freiburg, FRG.