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Ionizing radiation regulates expression of the c-*jun* protooncogene

(transcription factors/AP-1/c-*fos*/*jun-B*/dose rate)

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ABSTRACT **There is little known about the regulation of gene expression by ionizing radiation exposure. The present studies demonstrate transcriptional activation of a mammalian gene, the c-*jun* protooncogene, by x-rays. The c-*jun* gene encodes a component of the AP-1 protein complex and is important in early signaling events involved in various cellular functions. The increase in c-*jun* transcripts by ionizing radiation was time- and dose-dependent as determined by Northern blot analysis. Transcriptional run-on analysis demonstrated that ionizing radiation stimulates the rate of c-*jun* gene transcription. Furthermore, the half-life of c-*jun* RNA was prolonged in the absence of protein synthesis. These findings indicate that the increase in c-*jun* RNA observed after irradiation is regulated by transcriptional and posttranscriptional mechanisms. Moreover, the induction of c-*jun* by ionizing radiation was associated with an inverse dose rate effect in that decreasing the dose rate resulted in increased c-*jun* expression. The present results similarly demonstrate that ionizing radiation increases levels of c-*fos* transcripts as well as that of *jun-B*, another member of the *jun* family. Taken together, these results suggest a role for induction of early response genes in the pathophysiologic effects of ionizing radiation.**

AP-1, the product of the protooncogene c-*jun*, recognizes and binds to specific DNA sequences and stimulates transcription of genes responsive to certain growth factors and phorbol esters (1, 2). The expression of c-*jun* is an early response event during activation of cellular proliferation. For example, expression of c-*jun* is regulated by serum, platelet-derived growth factor, fibroblast growth factor, epidermal growth factor, nerve growth factor, transforming growth factor β, interleukin 1, and tumor necrosis factor (3–11). The product of the c-*jun* protooncogene contains a highly conserved DNA binding domain shared by a family of mammalian transcription factors, including *jun-B*, *jun-D*, c-*fos*, *fos-B*, *fra-1*, as well as the yeast GCN4 protein. The conserved leucine zipper allows for dimerization between certain members of this family, whereas the basic motif is necessary for binding to the phorbol ester responsive element (12—16). Specific protein heterodimeric complexes contribute to the DNA binding affinity (17–21).

Ionizing radiation has been postulated to induce multiple biological effects by direct interaction with DNA or through the formation of free radical species leading to DNA damage (22). These effects include gene mutations, malignant transformation, and cell killing. Although ionizing radiation has been demonstrated to induce expression of certain DNA repair genes in some prokaryotic and lower eukaryotic cells, little is known about the effects of ionizing radiation on the regulation of mammalian gene expression (23). Several studies have described changes in the pattern of protein synthesis observed after irradiation of mammalian cells. For example, ionizing radiation treatment of human malignant melanoma cells is associated with induction of several unidentified proteins (24). Synthesis of cyclin and coregulated polypeptides is suppressed by ionizing radiation in rat REF52 cells but not in oncogene-transformed REF52 cell lines (25). Other studies have demonstrated that certain growth factors or cytokines may be involved in x-ray-induced DNA damage. In this regard, platelet-derived growth factor is released from endothelial cells after irradiation (26), whereas increased production of tumor necrosis factor is associated with ionizing radiation treatment in human sarcoma cells (27). Recent work has also shown that interleukin 1 RNA is increased after irradiation of Syrian hamster embryo cells (28).

Initiation of mRNA synthesis is a critical control point in the regulation of cellular processes and depends on binding of certain transcriptional regulatory factors to specific DNA sequences. However, there is little known about the regulation of transcriptional control by ionizing radiation exposure in eukaryotic cells. The effects of ionizing radiation on posttranscriptional regulation of mammalian gene expression are also unknown. In the present studies, we have examined the effects of ionizing radiation on the regulation of c-*jun* gene expression. The results demonstrate that ionizing radiation transcriptionally regulates c-*jun* expression. Furthermore, c-*jun* transcripts are degraded posttranscriptionally by a labile protein in irradiated cells. The results similarly demonstrate that c-*fos* and *jun-B* gene expression, other members of a family of transcription factors with related DNA binding specificity, is increased following exposure to ionizing radiation.

MATERIALS AND METHODS

Cell Culture. Human HL-60 promyelocytic leukemia cells, U-937 monocytic leukemia cells (both from American Type Culture Collection), and AG-1522 diploid foreskin fibroblasts (National Institute on Aging Cell Repository, Camden, NJ) were grown as described (27, 29). Cells were irradiated using either a Philips RT 250 accelerator at 250 kV, 14 mA equipped with a 0.35-mm Cu filter or a Gammacell 1000 (Atomic Energy of Canada, Ottawa) with a ^{137}Cs source emitting at a fixed dose rate of 14.3 Gy/min as determined by dosimetry. Control cells were exposed to the same conditions but not irradiated.

Northern Blot Analysis. Total cellular RNA was isolated as described (29). RNA (20 μg per lane) was separated in an agarose/formaldehyde gel, transferred to a nitrocellulose filter, and hybridized to the following ^{32}P-labeled DNA probes: (*i*) the 1.8-kilobase (kb) *Bam*HI/*Eco*RI c-*jun* cDNA (30); (*ii*) the 0.91-kb *Sca* I/*Nco* I c-*fos* DNA consisting of exons 3 and 4 (31); (*iii*) the 1.8-kb *Eco*RI *jun-B* cDNA isolated from the p465.20 plasmid (32); and (*iv*) the 2.0-kb *Pst* I β-actin cDNA purified from pA1 (33). The autoradiograms were

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scanned using an LKB UltroScan XL laser densitometer and analyzed using the LKB GelScan XL software package. The intensity of c-*jun* hybridization was normalized against β-actin expression.

Run-On Transcriptional Analysis. HL-60 cells were treated with ionizing radiation and nuclei were isolated after 3 h as described (29). Newly elongated ^{32}P-labeled RNA transcripts were hybridized to plasmid DNAs containing various cloned inserts after digestion with restriction endonucleases as follows: (*i*) the 2.0-kb *Pst* I fragment of the chicken β-actin pA1 plasmid (positive control); (*ii*) the 1.1-kb *Bam*HI insert of the human β-globin gene (negative control, ref. 34); and (*iii*) the 1.8-kb *Bam*HI/*Eco*RI fragment of the human c-*jun* cDNA from the pBluescript SK(+) plasmid. The digested DNA was run in a 1% agarose gel and transferred to nitrocellulose filters by the method of Southern. Hybridization was performed with 10^7 cpm of ^{32}P-labeled RNA per ml of hybridization buffer for 72 h at 42°C. Autoradiography was performed for 3 days and the autoradiograms were scanned as already described.

RESULTS AND DISCUSSION

Induction of c-*jun* RNA by Ionizing Radiation. To determine the effects of ionizing radiation on c-*jun* expression, we performed Northern blot analyses of HL-60 cellular RNA using a ^{32}P-labeled c-*jun* cDNA probe. The level of the 2.7-kb c-*jun* transcripts increased 9.6-fold 3 h after exposure to ionizing radiation (Fig. 1*A*). This increase was transient and the level of c-*jun* transcripts returned to that of control cells by 24 h (Fig. 1*A*). The induction of c-*jun* gene expression was also dependent on the dose of radiation. Although detectable increases in c-*jun* expression were observed with 5 Gy, maximal c-*jun* mRNA levels were detectable after 50 Gy of ionizing radiation (Fig. 1*B*). In contrast, ionizing radiation had no effect on levels of actin transcripts. Similar kinetics of c-*jun* induction were observed in irradiated human U-937 monocytic leukemia cells (Fig. 2*A*) and in normal human AG-1522 diploid fibroblasts (Fig. 2*B*). Treatment of AG-1522 cells with ionizing radiation was also associated with the appearance of a minor 3.2-kb c-*jun* transcript (Fig. 2*B*).

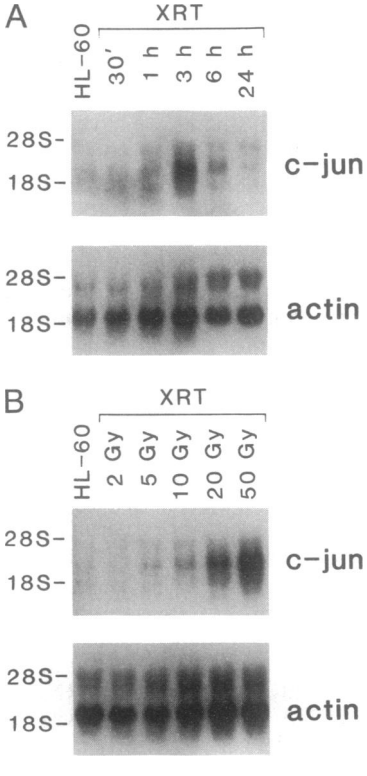

FIG. 1. Effects of ionizing radiation on c-*jun* RNA levels in human HL-60 cells. (*A*) Northern blot analysis of total cellular RNA levels was performed in HL-60 cells after treatment with 20 Gy of ionizing radiation (XRT). Hybridization was performed using a ^{32}P-labeled c-*jun* or actin DNA probe. (*B*) HL-60 cells were treated with the indicated doses of ionizing radiation. RNA was isolated after 3 h and hybridizations were performed using ^{32}P-labeled c-*jun* or β-actin DNA probes. HL-60 represents RNA from untreated cells.

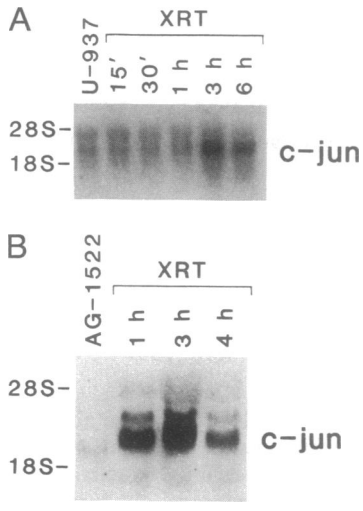

FIG. 2. Effects of ionizing radiation on c-*jun* RNA levels in U-937 cells and in human AG-1522 diploid fibroblasts. (*A*) Northern blot analysis of RNA levels was performed in U-937 cells after treatment with 20 Gy of ionizing radiation (XRT). Hybridization was performed using a ^{32}P-labeled c-*jun* or actin DNA probe. (*B*) AG-1522 cells were treated with 20 Gy of ionizing radiation. RNA was isolated at the indicated times and hybridizations were performed using a ^{32}P-labeled c-*jun* probe. Hybridization to the ^{32}P-labeled 7S rRNA probe (27) demonstrated slight overloading of the first lane corresponding to RNA from untreated AG-1522 cells.

Transcriptional Activation of c-*jun* by Ionizing Radiation. Run-on transcriptional assays in isolated nuclei were performed to determine the mechanisms responsible for the regulation of c-*jun* gene expression by ionizing radiation. The actin gene (positive control) was constitutively transcribed in untreated HL-60 cells, whereas there was no detectable level of β-globin gene transcription (negative control) (Fig. 3). In contrast, a low level of c-*jun* transcription was detectable in untreated HL-60 cells (Fig. 3). Exposure to ionizing radiation increased c-*jun* gene transcription by 7.2-fold (Fig. 3). Furthermore, there was no detectable effect on actin gene transcription in irradiated cells. These findings indicated that ionizing radiation induces c-*jun* expression, at least in part, by a transcriptional mechanism.

Posttranscriptional Regulation of c-*jun*. Increased levels of c-*jun* RNA in cells exposed to serum, phorbol esters, or

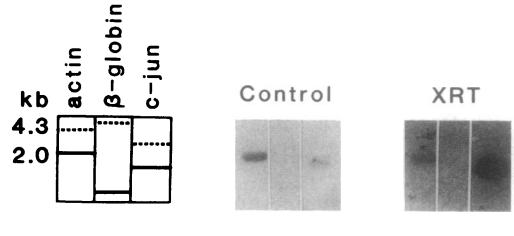

FIG. 3. Effects of ionizing radiation on rates on c-*jun* gene transcription. HL-60 cells were treated with 20 Gy of ionizing radiation (XRT) and nuclei were isolated after 3 h. Newly elongated ^{32}P-labeled RNA transcripts were hybridized to plasmid DNAs containing 2 μg of β-actin, β-globin, and c-*jun* cDNA. In the schematic diagram, the solid lines represent the relative positions of the cDNA inserts, and the dashed lines indicate the positions of the plasmid vectors.

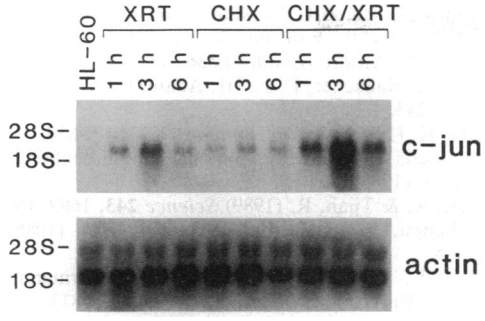

FIG. 4. Effects of cycloheximide on c-*jun* mRNA levels in ionizing radiation-treated HL-60 cells. HL-60 cells were treated with 20 Gy of ionizing radiation (XRT) and/or 5 μg of cycloheximide (CHX) per ml. Total cellular RNA (20 μg per lane) was isolated after 1, 3, and 6 h and analyzed by hybridization to the ^{32}P-labeled c-*jun* or actin probe.

certain growth factors also result from enhanced stabilization of the c-*jun* transcript. In order to study posttranscriptional regulation of c-*jun* RNA, HL-60 cells were treated with ionizing radiation in the absence and presence of cycloheximide. Cycloheximide alone had a slight but detectable effect on the accumulation of c-*jun* RNA. However, the combination of cycloheximide and ionizing radiation increased levels of c-*jun* by 3.6-fold as compared to treatment with radiation alone (Fig. 4), suggesting that the effects of this combination were least additive in these cells. These results also indicated that *de novo* protein synthesis is not required for the induction of c-*jun* by ionizing radiation. Furthermore, cycloheximide had no effect on c-*jun* transcription at 3 h as monitored by nuclear run-on assays (data not shown). These results suggested that cycloheximide increases c-*jun* expression by a posttranscriptional mechanism in irradiated cells.

To further study the posttranscriptional regulation of ionizing radiation-induced c-*jun* RNA levels, HL-60 cells were irradiated to induce c-*jun* expression after 3 h and then exposed to 5 μg of actinomycin D per ml for various times to inhibit further transcription. The half-life of c-*jun* RNA as determined by densitometric scanning was ≈58 min. In contrast, inhibition of protein synthesis with cycloheximide in the absence of transcription increased the half-life of c-*jun* RNA in irradiated HL-60 cells to 94 min. Taken together, these findings suggested that the increase in c-*jun* RNA observed during radiation treatment is also mediated at least in part by posttranscriptional mechanisms involving the synthesis of a labile protein that affects the turnover of c-*jun* RNA. This posttranscriptional regulation of c-*jun* mRNA levels may be related to the presence of (A+U)-rich sequences in the 3′ untranslated region of its mRNA (30). These sequences mediate selective processing and degradation of mRNAs for other protooncogenes as well as cytokines (35). The regulation of c-*jun* by ionizing radiation is thus in certain respects similar to that observed for serum and growth factors.

Induction of c-*fos* and *jun-B* by Ionizing Radiation. The protein product of c-*jun* contains a DNA binding region that is shared by members of a family of transcription factors (36, 37). Specific protein complexes enhance DNA binding affinity (15, 18). For example, Jun and Fos proteins form heterodimeric complexes with a higher DNA binding affinity than Jun protein homodimers (13). Further studies were thus performed to determine the effects of ionizing radiation on c-*fos* gene expression. Although *c-fos* RNA was present at low levels in untreated HL-60 cells, treatment with ionizing radiation was associated with a dose-dependent increase in c-*fos* transcripts (Fig. 5*A*). This increase in c-*fos* expression was maximal at 3 h after irradiation and associated with down-regulation of c-*fos* RNA levels by 24 h (Fig. 5*A* and data not shown). Similar effects were also observed with other

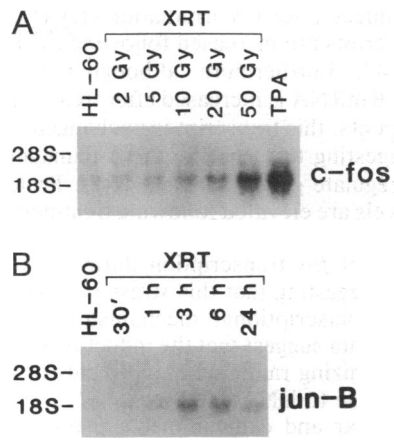

FIG. 5. Effects of ionizing radiation on c-*fos* and *jun-B* mRNA levels in HL-60 cells. (*A*) HL-60 cells were treated with varying doses of ionizing radiation (XRT) or 32 nM 12-*O*-tetradecanoylphorbol 13-acetate (TPA; positive control) for 3 h. Total cellular RNA (20 μg) was hybridized to the ^{32}P-labeled c-*fos* probe. (*B*) HL-60 cells were treated with 20 Gy of ionizing radiation. Total cellular RNA (20 μg per lane) was isolated at the indicated times and analyzed by hybridization to the ^{32}P-labeled *jun-B* probe.

members of the *jun* family. In this regard, ionizing radiation treatment was associated with increases in *jun-B* mRNA levels that were maximal at 3 h (Fig. 5*B*).

Dose Rate Effect on c-*jun* Expression. The effects of ionizing radiation on DNA damage and cell killing in many models are proportional to the dose rate. For example, increasing the dose rate in mouse jejunal crypt cells irradiated with γ-rays from a ^{137}Cs source is associated with increased cell killing (38). Consequently, we examined the effects of the dose rate on c-*jun* expression. Decreasing the dose rate from 14.3 Gy/min to 0.67 Gy/min was associated with increases in the induction of c-*jun* transcripts (Fig. 6). A similar inverse dose rate effect of irradiation on c-*jun* expression was observed for total doses of 10 or 20 Gy (Fig. 6). Experiments comparing cell survival and transformation in C3H/10T½ cells demonstrate a decrease in cell killing and transformation when low dose rate exposures to ^{60}Co radiation were compared to high dose rate exposures (39). Induction of relatively error-free DNA repair processes by low dose rate, low linear energy transfer radiation, has been suggested as an explanation for these effects (39, 40). Perhaps the c-*jun* gene product initiates a cascade of DNA repair genes that enhances cell survival and decreases transformation. However, the mechanism and the significance of increased transcription of c-*jun* at the lower dose rate is as yet unknown.

Certain other genes may also play a role in the cellular response to stress or DNA-damaging agents. For example, metallothionein I and II, collagenase, and plasminogen acti-

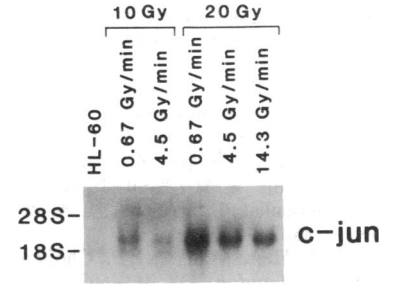

FIG. 6. Effects of dose rate on the induction of c-*jun* expression by ionizing radiation. HL-60 cells were treated with 10 or 20 Gy of ionizing radiation at the indicated dose rates. After 3 h, total cellular RNA (20 μg) was isolated and hybridized to the ^{32}P-labeled c-*jun* probe.

vator are induced after UV irradiation (41–45). B2 polymerase III transcripts are increased following treatment by heat shock (46, 47). Furthermore, although the level of DNA polymerase β mRNA is increased after treatment with DNA-damaging agents, this transcript is unchanged following irradiation, suggesting that specific DNA-damaging agents differentially regulate gene expression (48). Protooncogene c-*fos* RNA levels are elevated following treatment by UV, heat shock, or chemical carcinogens (49, 50). In this regard, the relative rates of *fos* transcription during heat shock were unchanged, suggesting that this stress increased c-*fos* RNA through posttranscriptional mechanisms (50). Taken together, these data suggest that the induction of the *jun* family of genes by ionizing radiation may be part of a generalized cellular response to DNA damage.

The molecular and cellular mechanisms responsible for DNA damage-induced growth arrest are poorly understood (23). Our observation that the c-*jun* early response gene as well as other members of this multigene family are induced by ionizing radiation suggests that activation of this gene may be involved in signal transduction mechanisms that initiate pleiotropic cellular responses to x-ray exposure such as DNA repair, transformation, and inhibition of cell cycle progression. The target gene(s) activated by Jun/AP-1 following exposure to ionizing radiation are unknown. However, tumor necrosis factor is released from cells following irradiation (22). Preliminary studies indicate that the increase in tumor necrosis factor following ionizing radiation treatment is associated with transcriptional activation (M.L.S., unpublished data). The 5′ promoter region of the tumor necrosis factor gene contains sequences with homology to a Jun/AP-1 site (51). However, it is not clear whether this site binds AP-1 and if it is involved in the regulation of tumor necrosis factor gene expression (51). Recent studies have demonstrated UV-responsive elements in the human immunodeficiency virus type 1, collagenase, c-*fos*, and metallothionein genes (52). Experiments are now needed to identify the potential role of cis elements involved in the induction of gene expression by ionizing radiation.

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