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c-*fos* mRNA Expression in Macrophages Is Downregulated by Interferon-γ at the Posttranscriptional Level

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Treatment of macrophages with interferon-γ (IFNγ) strongly decreased the induction of c-*fos* mRNA by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), lipopolysaccharide, or calcium ionophore A23187 in macrophages. Under the same experimental conditions, IFNγ induced oligo(A) synthetase mRNA and did not affect the constitutive expression of transforming growth factor β mRNA, indicating that IFNγ did not induce general degradation of mRNAs. Run-on experiments indicated that c-*fos* was constitutively transcribed at low levels and that TPA augmented c-*fos* transcription. IFNγ did not inhibit constitutive or TPA-induced c-*fos* transcription. However, IFNγ decreased c-*fos* mRNA stability, as assessed by measuring the half-life of c-*fos* mRNA in actinomycin D-treated cells. These results indicated that IFNγ inhibited c-*fos* mRNA induction by TPA at the posttranscriptional level.

Macrophages and monocytes activated by interferon-γ (IFNγ) express new or augmented biological functions, including tumoricidal activity (1, 19, 23, 28, 35). The activation of tumoricidal macrophages by IFNγ is not sensitive to cycloheximide (2) and does not require active protein kinase C (26). Interferons induce expression of many genes, such as the 2′-5′oligo(A) synthetase gene (8, 16–18, 22) and the major histocompatibility complex gene cluster (3, 9, 30), a cluster composed of at least six genes located on chromosome 1 (5) whose functions are still under investigation. Moreover, macrophages but not other cell types such as fibroblasts respond to IFNγ with alteration in the maturation of rRNA. We have shown that the activation of macrophages by IFNγ induces a block of rRNA maturation concomitant with an increase in the steady-state levels of the 45S, 41S, and 36S rRNA precursors (25, 34). These data provided an indication that IFNγ could control macrophage gene expression at a posttranscriptional level. Peritoneal macrophages have a low but significant constitutive expression of c-*fos* mRNA that can be augmented by protein kinase C agonists, including 12-*O*-tetradecanoylphorbol-13-acetate (TPA), 1-oleolyl-2-acetoyl glycerol, calcium ionophore A23187 (CaI), and cytokines, or by endotoxins (14, 24, 31). Since IFNγ does not induce c-*fos* in macrophages but can modulate the expression of other cellular genes (13, 25), we investigated whether IFNγ can modulate the induction of c-*fos* by other agents. For these studies we took advantage of macrophage cell lines that we have immortalized from mouse bone marrow. One cloned cell line, designated ANA-1, was developed from the bone marrow of C57BL/6 mice, the same strain from which the fresh peritoneal macrophages were used in these studies. ANA-1 cells were characterized in detail previously (6). The availability of this cell line allowed us to perform nuclear run-on assays to examine the effects of IFNγ on a homogeneous cell population and to extend our observations on peritoneal macrophages to the proliferating cells. We found that IFNγ inhibited the augmentation of c-*fos* mRNA by TPA, lipopolysaccharide (LPS), or CaI, demonstrating that IFNγ is a negative signal for c-*fos* mRNA augmentation in macrophages.

MATERIALS AND METHODS

Macrophages. Peritoneal exudate cells were harvested 4 days after mice were injected intraperitoneally with 1 ml of 1% thioglycolate medium and plated as described previously (24). The ANA-1 macrophage cell line, generated from the bone marrow of C57BL/6N mice, was previously described in detail (6).

Reagents. TPA, LPS, CaI, and actinomycin D (DAct) were purchased from Sigma Chemical Co. (St. Louis, Mo.). Recombinant murine IFNγ was purchased from Amgen Biologicals (Thousand Oaks, Calif.).

RNA extraction and analysis. After 18 h of incubation with medium or IFNγ, macrophages were treated for 30 min with 30 nM TPA, 1 μg of LPS per ml, or 3 μM CaI and then solubilized with guanidine isothiocyanate (Bethesda Research Laboratories, Inc., Gaithersburg, Md.). The total RNA was purified by centrifugation through a cushion of CsCl according to the method of Chirgwin et al. (4). Purified RNA was separated on 1.2% agarose gels containing 2.2 M formaldehyde as previously described (32). The following probes were used: v-*fos* probe, 1-kb *Pst*I fragment (kindly provided by T. Curran [7]); 2′-5′oligo(A) synthetase (kindly provided by J. Chebath, Weitzmann Institute, Rehevot, Israel); and transforming growth factor beta (TGFβ) (kindly provided by R. Derynck, Genentech Inc., South San Francisco, Calif.).

Nuclear run-on assay. Nuclear run-on experiments were performed as described by Greenberg and Ziff (11). ANA-1 cells were cultured for 18 h in the presence or absence of IFNγ and then activated with 30 nM TPA for 5, 10, 15, 20, 30, 40, 50, and 60 min. Trichloroacetic acid-precipitable counts (2×10^6 cpm/ml) were hybridized to *fos*, TGFβ, or pBR322 DNA probes spotted on nitrocellulose.

RESULTS

Experiments were performed to determine the effects of IFNγ on the augmentation of c-*fos* mRNA by TPA, LPS, or CaI in nonproliferating fresh peritoneal macrophages. Peri-

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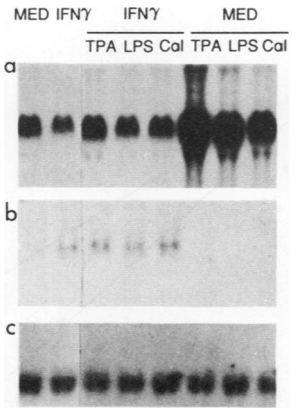

FIG. 1. Effects of IFNγ on the induction of c-*fos* (a), oligo(A) synthetase (b), and TGFβ (c) mRNAs. Peritoneal macrophages at 10^6 cells per ml were treated with 100 U of IFNγ per ml for 18 h at 37°C and then with 30 nM TPA, 1 μg of LPS per ml, or 3 μM CaI, as indicated. The cells were further incubated for 30 min at 37°C, and total RNAs were extracted and analyzed by Northern blot for c-*fos* mRNA expression. MED, Medium.

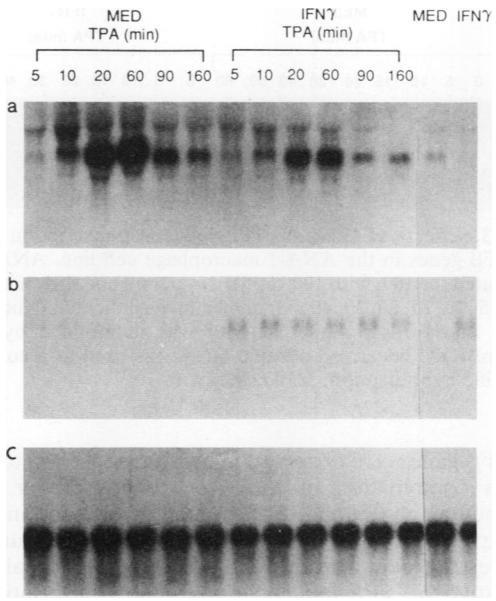

FIG. 2. Influence of IFNγ treatment on the kinetics of c-*fos*, oligo(A) synthetase, and TGFβ mRNA expression in response TPA in ANA-1 macrophages. ANA-1 cells were cultured for 18 h in medium (MED) or in medium containing 100 U of IFNγ per ml (IFNγ) and then treated for 5, 10, 20, 60, 90, or 160 min with 30 nM TPA, as indicated. Total RNAs were isolated, purified, and analyzed by Northern blot for c-*fos* mRNA (a), 2′-5′oligo(A) synthetase mRNA (b), or TGFβ mRNA (c).

toneal macrophages were cultured for 18 h in the presence or absence of IFNγ (100 U/ml) and then stimulated for 30 min with 30 nM TPA, 1 μg of LPS per ml, or 3 μM CaI. As shown by the results of Northern (RNA) blot analysis depicted in Fig. 1, c-*fos* mRNA expression was augmented by TPA, LPS, or CaI in peritoneal macrophages cultured for 18 h in regular medium. However, in peritoneal macrophages exposed to 100 U of IFNγ per ml, the expression of c-*fos* mRNA in response to TPA, LPS, or CaI was four- to sixfold lower (Fig. 1a). IFNγ treatment also caused some decrease (1.5- to 2-fold) in the constitutive expression of c-*fos* mRNA. As shown in Fig. 1b, peritoneal macrophages constitutively expressed low levels of 2′-5′oligo(A) synthetase mRNA. IFNγ treatment significantly augmented the 2′-5′oligo(A) synthetase mRNA levels in macrophages. TPA, LPS, or CaI alone or following IFNγ did not affect the expression of the 2′-5′oligo(A) synthetase mRNA. The same RNAs were also tested for TGFβ mRNA expression. As shown in Fig. 1c, TGFβ mRNA expression was not altered by IFNγ alone or in combination with TPA, LPS, or CaI. These results demonstrated that expression of c-*fos* mRNA in response to LPS, TPA, or CaI was selectively inhibited in macrophages activated by IFNγ. However, this phenomenon was not due to a general decrease in mRNA levels, since IFNγ induced 2′-5′oligo(A) synthetase mRNA and did not affect the constitutive expression of TGFβ mRNA.

To investigate the kinetics of the effects of IFNγ on c-*fos* mRNA induction, peritoneal macrophages were treated with IFNγ for 2, 4, 12, and 18 h and the expression of c-*fos* mRNA in response to TPA was tested. The inhibition by IFNγ of c-*fos* mRNA was time dependent. Two hours of IFNγ treatment caused a 23% decrease of c-*fos* mRNA induction by TPA, and inhibitory effects of IFNγ increased at 4 h (about 50% of inhibition) and reached plateau level (about 85% inhibition) between 12 and 18 h of macrophage exposure to IFNγ (data not shown).

Experiments were also performed on the ANA-1 macrophage cell line to investigate whether IFNγ could affect c-*fos* mRNA expression in proliferating macrophages. Treatment of ANA-1 cells or peritoneal macrophages for 18 h with 100 U of IFNγ per ml inhibited the ability of TPA to augment c-*fos* mRNA to a similar extent (data not shown), indicating that IFNγ can inhibit the induction of c-*fos* mRNA in fresh macrophages and in macrophage cell lines.

The inhibitory effects of IFNγ on c-*fos* mRNA induction can be accounted for by changes in the kinetics of c-*fos* mRNA expression, c-*fos* mRNA transcription, or half-life of c-*fos* mRNA. To investigate whether the kinetics of c-*fos* mRNA augmentation by TPA are altered by IFNγ, ANA-1 macrophages were cultured for 18 h in the presence or absence of 100 U of IFNγ per ml and then treated for 5, 10, 20, 60, 90, or 160 min with 30 nM TPA. As shown in Fig. 2, we consistently observed a peak of c-*fos* mRNA induction between 20 and 60 min of TPA treatment in IFNγ-treated and untreated macrophages, followed by a gradual return to the basal level. Lower levels of c-*fos* mRNA expression were consistently observed at every time after TPA treatment in IFNγ-treated macrophages. As shown in Fig. 2b, IFNγ augmented oligo(A) synthetase mRNA expression and TPA did not affect this response. When the blot was probed for TGFβ mRNA, no changes in TGFβ mRNA expression were observed (Fig. 2c).

Overall, these data suggest that IFNγ did not cause the major alteration in the kinetics of c-*fos* mRNA expression in response to TPA.

To establish whether the IFNγ-inhibited c-*fos* mRNA expression was at the level of transcription in ANA-1 cells, nuclear run-on assays were performed. As shown in Fig. 3, c-*fos* was constitutively transcribed in ANA-1 cells and TPA treatment enhanced the transcription within 5 min. However, pretreatment of ANA-1 cells with IFNγ for 18 h did not affect the constitutive levels or the TPA-induced c-*fos* transcription. As an internal control in the assay, we measured TGFβ gene transcription. No changes in the transcription of

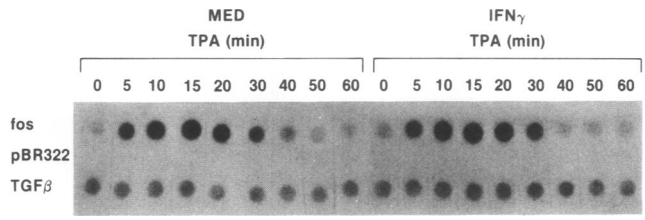

FIG. 3. Effects of IFNγ on TPA-induced transcription of c-*fos* and TGFβ genes in the ANA-1 macrophage cell line. ANA-1 cells were treated for 18 h with 100 U of IFNγ per ml and then with 30 nM TPA for 5, 10, 15, 20, 30, 40, 50, or 60 min, as indicated. Nuclei were isolated, and transcriptional activity was determined by run-on assays. pBR322 linearized plasmid DNA was used as a control for nonspecific hybridization. MED, Medium.

the TGFβ gene were observed in response to TPA, to IFNγ, or to a combination of the two stimuli. Under similar experimental conditions, background hybridization of the transcripts with pBR322 was undetectable. In summary, these results demonstrated that IFNγ did not alter the constitutive or TPA-induced c-*fos* gene transcription and suggested that the decrease of c-*fos* mRNA expression by IFNγ may be due to posttranscriptional events.

To measure the half-life of c-*fos* mRNA, ANA-1 macrophages were cultured for 18 h in medium with or without 100 U of IFNγ per ml. They were then exposed to 30 nM TPA and treated with 5 μg of DAct per ml to block RNA synthesis. We found a faster decay of TPA-induced c-*fos* mRNA in IFNγ-activated macrophages than of the control. The half-life of c-*fos* mRNA induced by TPA in IFNγ-treated macrophages (27 min) was about 10 min shorter than the half-life of c-*fos* mRNA induced by TPA in untreated macrophages (37 min) (Fig. 4).

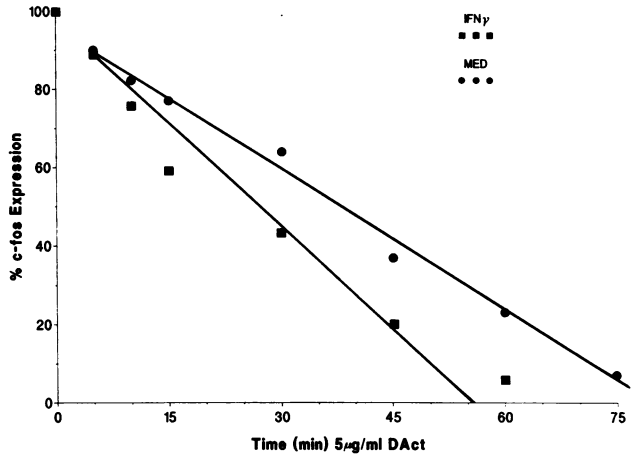

FIG. 4. Evaluation of the half-life of c-*fos* mRNA augmented by TPA in ANA-1 macrophages cultured in the presence or absence of IFNγ. ANA-1 cells cultured for 18 h in medium or in medium supplemented with 100 U of IFNγ per ml were treated with TPA and then with DAct (5 μg/ml) for 5, 10, 15, 30, 45, 60, or 75 min; 15 μg of total RNAs of untreated macrophages and 40 μg of total RNAs from IFNγ-treated macrophages were used to determine c-*fos* mRNA expression by laser scanning of Northern blot pictures. c-*fos* expression induced by 30 min of treatment with 30 nM TPA in untreated macrophages was plotted as 100% for a group designated MED, and c-*fos* expression induced by 30 min of treatment with 30 nM TPA in IFNγ-treated macrophages was considered as 100% for a group designated IFNγ. Levels of c-*fos* mRNA expression after 5, 10, 15, 30, 45, 60, or 75 min of Dact treatment were calculated and plotted as percent expression compared with 100% of c-*fos* mRNA for IFNγ-treated and untreated macrophages, respectively.

DISCUSSION

Many reports, including our own, indicated the occurrence of an increase in c-*fos* mRNA in macrophages and monocytes in response to TPA, LPS, colony-stimulating factor 1, and 1-oleolyl-2-acetoyl glycerol (14, 20–22, 24, 27). In contrast, neither IFNβ nor IFNγ augmented c-*fos* mRNA expression in macrophages (24), although they can induce c-*fos* mRNA expression in fibroblasts (36). In this study we report that IFNγ inhibited the augmentation of c-*fos* mRNA by TPA, CaI, and LPS. Similar inhibition was observed in fresh peritoneal macrophages as well as in the ANA-1 macrophage cell line. The observation that IFNγ can inhibit c-*fos* mRNA accumulation in fresh, nonproliferating peritoneal macrophages argues against the possibility that the observed downregulation of c-*fos* mRNA accumulation is secondary to the IFNγ-induced inhibition of cell proliferation.

Run-on experiments indicated that the transcriptional activation of c-*fos* mRNA by TPA was not affected by treatment with IFNγ and that the rapid induction and shutoff of c-*fos* transcription were observed both in the presence and in the absence of IFNγ. These results demonstrated that inhibition of c-*fos* mRNA expression by IFNγ cannot be accounted for by a decrease in transcriptional activity. Moreover, the normal rate of c-*fos* transcriptional activity in IFNγ-treated macrophages demonstrated that the decrease in c-*fos* mRNA accumulation was not due to changes in the biochemistry of the TPA response, including the number or affinity of TPA receptors.

Thus, the decrease in the steady-state levels of c-*fos* mRNA can be due to inhibition of c-*fos* elongation (10), which does not affect the translation of the 5′ end of the c-*fos* and would not be very evident in our run-on assay, or by a decrease in mRNA stability. Evaluation of c-*fos* mRNA stability in DAct-treated cells demonstrated decreased stability of TPA-induced c-*fos* mRNA in IFNγ-treated cells. However, such a decrease in c-*fos* mRNA stability may not be of sufficient magnitude to account for the major decrease of c-*fos* mRNA steady-state level in IFNγ-treated cells. Therefore, either multiple mechanisms contributed to the inhibition of c-*fos* mRNA in response to IFNγ or the true half-life of c-*fos* mRNA could not be estimated by using DAct treatment as previously suggested (29). The half-life of c-*fos* mRNA in macrophages seems to be longer than that described in fibroblasts. This phenomenon could be caused by a differential effect of DAct on fibroblasts and macrophages, or it may reflect a true lineage difference. Consistent with the latter hypothesis, c-*fos* mRNA expression differs in many ways in these two lineages. As opposed to fibroblasts, c-*fos* expression in macrophages is not associated with cell proliferation (24), is inhibited rather than induced by IFNγ, and follows a slower kinetic of induction (this report). In conclusion, our results demonstrated that IFNγ inhibited c-*fos* mRNA expression downstream to the initiation of mRNA transcription and indicated that a decrease in c-*fos* mRNA stability could have been part of the inhibitory mechanism.

Our results also demonstrated that IFNγ can induce 2′-5′oligo(A) synthetase mRNA both in fresh macrophages and in a macrophage cell line. These results, in conjunction

with the observation that the constitutive levels of TGFβ mRNA were not affected by exposure of macrophages to any of the activation agents alone or in combination, indicated that the downregulation of c-*fos* mRNA was not the result of general degradation of mRNA in IFNγ-treated macrophages. Moreover, the inhibitory effect of IFNγ on c-*fos* expression seems to be lineage specific, perhaps restricted to monocytic cells, since it was shown that IFNγ alone can induce c-*fos* expression in fibroblasts (36).

IFNγ induces expression of many genes, including those encoding plasminogen activator (15) and class II major histocompatibility complex molecules (3, 9, 30). Therefore, the downregulation of c-*fos* mRNA expression by IFNγ seems to represent a rather selective effect of IFNγ on some RNAs. In addition to c-*fos* mRNA, c-*myc* and rRNA were shown to be modulated at the posttranscriptional level by IFNγ (13, 25, 34).

There is also evidence of posttranscriptional modulation of c-*fms* mRNA, granulocyte/macrophage colony-stimulating factor mRNA, and JE gene expression in macrophages activated by agents other than IFNγ (12, 31, 33, 37). An important role of posttranscriptional control of gene expression in macrophages may be due to the fact that these cells are terminally differentiated leukocytes, whose activation process is not associated with the clonal expansion seen in B or T lymphocytes. Thus, long-term transcriptional programming of gene expression may not be needed for the transient manifestation of the activated phenotype. Posttranscriptional control may be a more effective way to rapidly prevent the expression of genes which are not needed, or are perhaps inhibitory, for the expression of functional activities.

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