Inhibition of Mitochondrial Function by Interferon*

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John A. Lewis, Afroza Huq, and Pilar Najarro
From the Department of Anatomy and Cell Biology, SUNY Health Science Center at Brooklyn, Brooklyn, New York 11203

Interferons (IFNs) are cytokines that have multiple effects on cell function. In addition to blocking virus replication they exert regulatory effects on lymphocytes, modulate macrophage function, up-regulate major histocompatibility complex class I expression, and inhibit the growth of many different cell types (1). The molecular basis underlying most of these effects is presently not known, and only in the case of antiviral responses do we have a reasonable understanding of the mechanisms involved (2). In common with other cytokines IFNs exert their actions by modulating the expression of multiple genes whose products are responsible for the phenotypic changes observed after treatment. Identification of these genes and the mechanism by which their products function is needed to provide a complete understanding of cytokine action.

We reported earlier that type I IFNs caused a down-regulation of mitochondrial gene expression. We showed previously that type I interferon causes a down-regulation of mitochondrial gene expression. We show here that IFN treatment leads to functional impairment of mitochondria. Western blot analysis indicated that interferon treatment reduces the steady-state level of cytochrome b in murine L-929 cells. Interferon produced a reduction in cytochrome c oxidase and NADH-cytochrome c reductase activities of isolated mitochondria as well as inhibiting electron transport in isolated mitochondria and in intact cells. Several mitochondrial mRNAs are affected by interferon treatment in human Daudi lymphoblastoid cells, which are highly sensitive to the antiproliferative effects of interferon. Electron transport in Daudi cells was also inhibited by interferon both in intact cells and isolated mitochondria with a dose response identical to that for the antiproliferative response. In contrast, a Daudi strain resistant to the antiproliferative effects of interferon showed no down-regulation of mRNA expression and no inhibition of electron transport. Possibly as a consequence of the inhibitory effect on mitochondrial gene expression, treatment with interferon causes a reduction in cellular ATP levels. The inhibition of cellular growth by interferon may thus be partly a consequence of a reduction in cellular ATP levels.

Materials and Methods

Cells and IFNs—Mouse L-929 cells have been described previously (3) and were grown in minimal essential medium containing 4 g/liter glucose, 10% (v/v) newborn calf serum, and antibiotics (100 units/ml penicillin, 50 μg/ml streptomycin). Daudi human lymphoblastoid cells (CCL-213) were obtained from ATCC (Rockville, MD), and the IFN-resistant Daudi line was kindly provided by Dr. Berish Rubin (Dept. of Biology, Fordham University, Bronx, NY). Both Daudi lines were grown in RPMI 1640 medium containing 10% (v/v) fetal bovine serum and antibiotics. Human A-549 cells (ATCC clone CCL-185) were purchased from ATCC and grown in minimal essential medium containing 4 g/liter glucose, 10% (v/v) newborn calf serum, and antibiotics. All cultures were incubated at 37 °C in a 5% CO2, 95% air atmosphere. Growth of cells was determined by counting viable cells as determined by trypan blue exclusion. Cells were routinely tested for mycoplasma contamination using the Gen-Probe detection kit (Gen-Probe Inc., San Diego, CA). Powdered media were purchased from Life Technologies, Inc., and sera were obtained from BioWhittaker (Walkersville, MD). Murine IFN-α (a mixture of approximately 20% α and 80% β) was purchased from Lee Biomedical (San Francisco, CA) at a specific activity of 5 × 10^6 reference units/mg of protein. Human IFN-α (Well-feron) was kindly provided by Burroughs Wellcome at a specific activity of 2 × 10^6 reference units/mg of protein. Both IFNs were titered in this laboratory as described elsewhere (11) on L-929 cells (for murine) and A-549 cells (for human) using Vescular Stomatitis Virus as the challenge.

Western Blot Analysis for Cytochrome b—Antibodies capable of recognizing murine cytochrome b were raised by immunizing rabbits with a conjugated peptide. The synthetic peptide represents a hydrophilic portion of murine cytochrome b with the sequence SNNPTGLNS-14, 21, and 49. Animals were bled and sera were prepared 7–14 days after boost with conjugated peptide. The conjugation was performed by coupling the peptide (synthesized with a C-terminal amide by Quality Biochemicals Inc., Hopkinton, MA) to keyhole limpet hemocyanin (a conjugated peptide). The antisera were raised by Cocalico Biologicals Inc. (Reamstown, PA). Western blot analysis was performed by preparing L-929 cell lysates in 1% Nonidet P-40, 0.25% sodium deoxycholate, 10 mM Tris-HCl, pH 7.5, 15 mM NaCl, 1.5 mM MgCl2, 1 mM phenylmethylsulfonyl fluoride, 15 units/ml aprotinin, and separating proteins by SDS-polyacrylamide gel electrophoresis (12). Proteins were transferred to nitrocellulose membranes (Schleicher & Schuell, Keene, ME) in Towbin’s buffer (20% methanol, 25 mM Tris-glycine, pH 8.3, 192 mM glycine-HCl) in a Bio-Rad transblotter (200 V for 45 min at 0 °C).

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‡To whom correspondence should be addressed: Dept. of Anatomy & Cell Biology, Box 5, SUNY Health Science Center at Brooklyn, 450 Clarkson Ave., Brooklyn, NY 11203. Tel.: 718-270-2215; Fax: 718-270-3732.

The abbreviations used are: IFN, interferon; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide.
Membranes were blocked by incubation in Tris-buffered saline (20 mM Tris-HCl, pH 7.6, 140 mM NaCl) containing 5% (v/v) nonfat dry milk (BLOTTO), 5% (v/v) goat serum (Sigma), and 0.1% (v/v) Tween 20 (Sigma). Membranes were incubated with antisera diluted 1:2,000 in the same solution at room temperature for 2 h. After washing, bound immunoglobulin was detected using the ECL kit (Amer sham Corp.). cDNA (RNA)–Total cell RNA was prepared and analyzed by Northern blotting as described previously (3). Plasmid BS-5 containing the murine cytochrome b cDNA (3) was labeled by nick translation (13) and used to detect cytochrome b mRNA. Hybridization conditions were as described before (3) except that incubations were performed at 42°C. The mRNAs for human COII and ATP6/8 were detected by hybridization to a nick-translated probe (plasmid ATCC number 61663) encompassing nucleotides 7392–8921 of the human mitochondrial genome (14). In this case hybridization was at 55°C as described elsewhere (3).

Preparation of Mitochondria and Measurement of Enzyme Activities—Cells were collected by tryps iniation and centrifugation (L-929) or centrifugation alone (Daudi) and washed in ice-cold phosphate-buffered saline. After resuspension in 1 ml per 2 × 10^7 cells of 10 mM Tris-HCl, pH 7.4, 10 mM NaCl, 1.5 mM CaCl_2, cells were swollen for 10 min at 4°C and ruptured by shearing in a Dounce homogenizer. An equal volume of 0.68 M sucrose, 20 mM Tris-HCl, pH 7.5, was added, and nuclei were removed by centrifugation at 1,000 × g for 10 min at 4°C (Sorvall SS-34 rotor). Mitochondria were sedimented at 17,000 × g for 10 min at 4°C and washed by resuspension in 0.34 M sucrose, 20 mM Tris-HCl, pH 7.5, 5.5 mM NaCl, 1 mM CaCl_2, followed by recentrifugation.

Cytochrome oxidase was assayed by the procedure of Cooper and Lazarow (15), and NADH cytochrome c reductase was assayed according to Schatz et al. (16). Reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) purchased from Sigma was assayed essentially as described by Slater et al. (17) by adding 30 μl of MTT (5 mg/ml) to 170 μl of mitochondrial extracts diluted in reaction buffer (35 mM KH_2PO_4, 5 mM MgCl_2, 2 mM KCN, 4 mM EDTA, 0.1 mM NADH) and incubating at 37°C for 15–30 min. After the addition of saturated (NH_4)_2SO_4 to stop the reaction, insoluble, reduced formazan was extracted with ethyl acetate, and the optical density at 550 nm was determined. For intact cells, the MTT assay was performed as described by Mosmann (18), and reduced formazan was extracted in 40 μl HCl/isopro pyl alcohol. For Daudi cells, suspensions were centrifuged at 17,000 × g for 10 min before extraction. Protein concentrations were measured by the BCA procedure (Pierce) using bovine serum albumin as a standard.

Measurement of Cellular ATP Levels—Cells were treated with IFN for the times indicated and then washed with ice-cold phosphate-buffered saline. After centrifugation, cells were resuspended in 1 ml per 2 × 10^7 cells of 40 mM Tris borate, pH 9.2, and an aliquot was removed for protein determination by either the BCA or Bradford (19) procedure using bovine serum albumin as a standard. After heating at 100°C for 3 min, precipitated proteins were removed by centrifugation, and the supernatants were used for ATP determination by the luciferin-luciferase technique. Briefly, equal volumes (100 μl) of sample diluted in 20 mM Hepes-KOH, pH 7.4, and luciferin-luciferase (Boehringer Mannheim or Sigma) were mixed, and luminescence was measured on a Monolight 2010 Luminometer (Analytical Luminescence Laboratory, San Diego, CA) for 2 s. ATP concentration was determined from a standard curve. Results were normalized for cell protein or number of cells.

RESULTS

IFN Causes a Reduction in Steady-state Mitochondrial Protein Level—Our earlier study showed that in addition to reducing the level of mitochondrial mRNAs, IFN inhibited the synthesis of mitochondrial proteins (3). To determine whether this reduced rate of synthesis resulted in a lower steady-state level of key mitochondrial proteins, an antipeptide antibody capable of recognizing murine cytochrome b was generated. Sera from rabbits injected with conjugated peptide were tested for reactivity against the peptide by enzyme-linked immunosorbent assay (not shown). Western blot analysis (Fig. 1) using this antibody showed that IFN caused a reduction in the level of a protein corresponding in size to cytochrome b (equal amounts of cellular protein were loaded on each lane). The effect of IFN was observed when cells were treated simultaneously and harvested with a paired control (left panel) or when cells were treated sequentially and harvested simultaneously (right panel). In control experiments, preincubation of the antibody with excess peptide blocked the binding to this protein (data not shown). This reduction became apparent within 24 h, indicating that the protein must turn over quite rapidly. Reduced levels of the protein were maintained for at least 72 h of treatment. Since IFN causes the down-regulation of all but one of the 13 mitochondrially encoded proteins at the RNA level it is highly probable that similar reductions in steady-state levels of other proteins occur.

IFN Inhibits Mitochondrial Electron Transport Activity—In order to assess whether this reduced level of mitochondrial proteins involved in electron transport leads to a decrease in mitochondrial functional activity we measured respiratory enzyme activity in isolated mitochondria. Mouse L-929 cells were treated with IFNα/β (500 units/ml) for 24 and 48 h, and mitochondrial fractions were prepared. Treatment with IFN caused a decrease in the activity of both NADH cytochrome c reductase and cytochrome c oxidase (Fig. 2). A reduction was seen by 24 h for NADH cytochrome c reductase (Fig. 2a), suggesting that the electron transport components turn over quite rapidly. A stronger reduction was seen by 48 h of treatment. Cytochrome c oxidase activity was also inhibited in mitochondria isolated from IFN-treated cells (Fig. 2b) although to a lesser extent. In agreement with this effect on enzymatic activity in isolated mitochondria, electron transport capability in intact L-929 cells was also inhibited by IFN (Fig. 3). Cells treated without or with IFN (500 units/ml) were incubated with the tetrazolium salt MTT, and the reduced, insoluble formazan product was extracted in 40% HCl and as a standard.

Effect of IFN on Mitochondrial mRNA Expression in Human Lymphoblastoid Daudi Cells—Mouse L-929 cells show relatively weak antiproliferative responses to IFN. In contrast, human Daudi lymphoblastoid cells are highly sensitive to IFN and have been used extensively in studies of the antiproliferative effects of IFN (21, 22). In Daudi cells, IFN-α causes an inhibition of cell growth that is detectable within 24 h and is quite marked by 48 h (Fig. 4a). IFN-α inhibits expression of cytochrome b mRNA in Daudi cells (Fig. 4, b and c). As shown in Fig. 4d, expression of other mitochondrial mRNAs (ATPas6/8 and COII) is also inhibited in these cells by IFN treatment. The levels of the mitochondrial mRNAs are reduced by 24 h after treatment in agreement with the kinetics of growth inhibition. Treatment of Daudi cells causes a reduction in actin mRNA levels (results not shown) and, to ensure equal loading of RNA, gels were therefore stained with ethidium bromide prior to blotting, and the 18 S RNA species is shown for comparison (Fig. 4). Unlike L-929 cells, which require IFN concentrations of 100 units/ml or greater to produce an antiproliferative effect, Daudi cells are sensitive to relatively low levels of IFN-α as shown in Fig. 5a, and a strong reduction in growth of Daudi cells is achieved with as little as 10 units/ml of IFN-α. Similarly, a reduction in the levels of mitochondrial cytochrome b mRNA has been detected with concentrations of IFN-α as

![Fig. 1. Effect of IFN-α on cytochrome b levels in L-929 Cells.](http://www.jbc.org/Downloaded from http://www.jbc.org/ by guest on July 8, 2017)
low as 10 units/ml (Fig. 4). Thus, unlike mouse L-929 cells, where relatively high IFN concentrations are needed for both antiproliferative responses and down-regulation of mitochondrial gene expression (3), both effects are observed at quite low levels of IFN in Daudi cells.

Inhibition of Mitochondrial Function in Daudi Cells—To determine whether a similar correlation exists between antiproliferative responses and effects on mitochondrial gene expression, the dose-response curve for inhibition of mitochondrial function was studied. Treatment with human IFN-α leads to an inhibition of cell growth even with doses as low as 10 units/ml (Fig. 5a). Electron transport in intact Daudi cells was inhibited by IFN-α with a very similar dose response curve (Fig. 5b). Electron transport activity in mitochondria isolated from IFN-α treated Daudi cells was also strongly inhibited with quite similar dose-response characteristics (Fig. 5c), showing that the effect on electron transport seen in intact cells is predominantly a result of an inhibition of mitochondrial function.

Inhibition of Mitochondrial Function Is Not a Consequence of Growth Inhibition—Although there appears to be a correlation between the antiproliferative response to IFN and the inhibition of mitochondrial function, it remained possible that the reduction in electron transport simply reflected reduced demand for energy generation. Daudi cells were cultured in medium with a reduced serum content, which gave rise to an inhibition of cell growth similar to that seen in IFN-treated cells (Fig. 6a). Despite the reduction in growth rate, electron transport activity in Daudi cells growing at low serum concentration was comparable with that of control cells and, in fact, showed an increased rate after prolonged serum deprivation (Fig. 6b). Thus, the effects of IFN on mitochondrial function cannot be ascribed to the reduction in the rate of proliferation.

Inhibition of Mitochondrial Function by IFN Correlates with Anti-proliferative Responses—In order to test whether a correlation between mitochondrial and anti-proliferative responses exists we studied the effect of IFN on an "IFN-resistant" strain of Daudi cells. DaudiPR cells show little or no growth inhibition in response to IFN-α (Fig. 7a). Moreover, as seen in Fig. 4d, no decrease in mitochondrial mRNAs was seen when DaudiPR cells were treated with IFN-α. Unlike the wild-type Daudi cells, no inhibition of electron transport was observed when DaudiPR cells were treated with IFN-α (500 units/ml) for 48 h (Fig. 7b).
Similarly, electron transport rates in mitochondria isolated from IFN-treated DaudiPR cells were unaffected (data not shown).

Treatment with IFN Causes a Decrease in Cellular ATP Levels—A decrease in mitochondrial functional capacity might be expected to reduce the rate of production of ATP. To determine whether cells treated with IFN contained lower levels of ATP, extracts were prepared and assayed by the luciferin-luciferase procedure. Mouse L929 cells treated with IFN-α showed a significant reduction in ATP levels (Table I). In contrast, cells cultured in medium containing a low serum concentration (0.2% in lieu of the normal 10% serum), and thus growth-inhibited, showed an increase in total ATP (25–50% after 48–72 h, data not shown). Similar experiments with Daudi cells (Table II) also showed that IFN-α caused a significant drop in cellular ATP levels. With Daudi cells the effect was more rapid and severe than in L-929 cells with a 50% decrease occurring within 24 h. The cellular ATP content was reduced to 20% of normal after 48 h and tended to recover somewhat at later times (as often observed for mRNA levels). However, serum depletion of Daudi cells again caused a significant increase in total ATP levels (127% after 48 h, data not shown).

Figure 4. Effect of IFN-α on proliferation and mitochondrial gene expression in human Daudi lymphoblastoid cells. Daudi cells in suspension culture were treated with human IFN-α (100 units/ml or as indicated) for the times shown. a. cell growth was determined by counting aliquots of cell suspension, b. time course for effect of IFN on mitochondrial mRNA levels. Daudi RNA was analyzed by Northern blotting using a probe against the murine mitochondrial cytochrome b gene. c. dose response curve for effect of IFN on mitochondrial mRNA levels. RNA was analyzed as above. d. Daudi and DaudiPR RNA was analyzed by Northern blotting for cytochrome b (as above) or ATP6 and cytochrome oxidase subunit II mRNA. At the bottom of each panel ethidium bromide staining of the gel is shown to indicate 18 S rRNA levels for normalization.

Figure 5. Effect of IFN-α on proliferation of Daudi cells and electron transport capability. Daudi cells were treated with IFN-α at the concentration shown for 40 h. a. growth was measured by counting cell suspensions; b. electron transport in intact cells was measured by reduction of MTT; c. electron transport in isolated mitochondria was measured by reduction of MTT. Values shown are mean ± S.D.
shown). This increase in ATP levels seen in serum-deprived cells may reflect reduced utilization for biosynthetic purposes with a normal capacity to generate ATP.

**DISCUSSION**

We showed previously that type I IFN causes a reduction in the levels of several mitochondrially encoded mRNAs in various cell lines. We have also shown that IFN has a similar effect on most of the 13 mitochondrial genes in L-929 cells (4). Reduced levels of mitochondrial mRNAs in Daudi cells have also been reported by Lou et al. (23). The reduction in mRNA levels was accompanied by a reduced level of synthesis of certain mitochondrially encoded proteins (4). These observations suggested that IFNs might exert certain actions by impairing mitochondrial function. Given the fundamental role of mitochondria in energy and nutrient metabolism this effect could play an important role in the antiproliferative responses to IFNs. The data presented here show that the reduced level of mitochondrial mRNAs and mitochondrial protein synthesis are in fact accompanied by a reduction in the steady-state level of key mitochondrial proteins such as cytochrome b. The level of this protein is reduced by approximately 50% by 48 h of IFN treatment, suggesting the possibility of functional impairment. The reduction in the amount of protein by 24 h suggests that cytochrome b has a relatively short half-life.

In agreement with the lower level of cytochrome b we observed a significant reduction in the electron transport capacity of IFN-treated cells. The activities of two of the principal complexes, NADH cytochrome c reductase and cytochrome oxidase, were strongly reduced within 24-48 h of treatment with IFN. Similar observations were made using reduction of MTT in both isolated mitochondria and intact cells. Even if some reduction of MTT in intact cells takes place via nonmitochondrial reactions, the similarity between our findings with specific enzymes and MTT reduction and between data for isolated mitochondria and intact cells clearly shows that IFN treatment causes an impairment of mitochondrial function. Lou et al. (23) reported previously that IFN treatment caused an impairment of oxygen consumption as measured 3 h after the addition of IFN. However, since these authors observed only a 30% (approximately) reduction in the levels of mRNA species after 9 h of treatment (23) it is not clear how electron transport could be affected so drastically within such a short time interval. IFN-γ is known to induce expression of nitric-oxide synthetase in macrophages, and this enzyme affects mitochondrial iron-sulfur containing enzymes, thus inhibiting mitochondrial function (24). However, type I IFNs do not induce nitric-oxide synthetase and in fact have been shown recently to inhibit its induction by IFN-γ (25).

IFN treatment also led to a decrease in cellular ATP in our studies. This effect is not due to the reduced rate of proliferation, since cells limited in growth by serum deprivation had a higher ATP level than normal cultures. If the level of ATP in cells limited in their growth by serum denpletion is taken as the actual control value, the effect of IFN is even more striking. It seems likely that the decreased mitochondrial electron transport activity in IFN-treated cells results in a lower capacity to generate ATP. Some cells, particularly tumor cells, devote a major fraction of ATP consumption to housekeeping functions rather than biosynthetic reactions (26, 27). In certain tumor cells the majority of glycolytic activity can be ascribed to the Na⁺K⁺-ATPase pump (27). Presumably ATP utilization for such roles is sufficient to deplete ATP levels in IFN-treated cells even though demand for growth-related purposes is reduced by the lower rate of proliferation. Cellular ATP levels are normally maintained at a constant level by modulation of oxidative phosphorylation activity and lactate production. It appears that in IFN-treated cells the defect in mitochondrial function becomes so severe that homeostasis can no longer be maintained.

The similarity between the dose dependence for the antiproliferative response and mitochondrial effects suggests that inhibition of mitochondrial function is at least partly responsible for the growth inhibition. This correlation is strengthened by results with the resistant DaudiPR cells, which show essen-
Interferon Inhibits Mitochondrial Function

Effect of interferon on ATP levels in Daudi cells

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Interferons and Other Regulatory Cytokines: A Practical Approach

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Effect of interferon on ATP levels in Daudi cells

Human Daudi cells were treated with IFN-α (100 reference units/ml) for the times shown and harvested, and both ATP and viable cell counts were determined. ATP levels are expressed as pmols of ATP per 10^6 cells. Values shown are means ± S.D. Data for two typical experiments are shown.

requires relatively high ATP concentrations (3 μM or greater) for maximal activity in vitro (28, 29). A 50% reduction in cellular ATP levels thus might cause some reduction of 2’,5’-oligo(A) synthesis in virus-infected cells. In contrast, the IFN-inducible, dsRNA-activated protein kinase PKR, has a K_m for ATP of 5 μM (30) in vitro and presumably would be unaffected by a 50% reduction in cellular ATP levels. On balance the reduction in ATP levels due to IFN is unlikely to impair the antiviral response significantly.

In a separate study we have shown that IFN down-regulates mitochondrial mRNAs at the transcriptional level. The mechanism underlying this effect is not known, but our data (3) support a model in which IFN stimulates the expression of a nuclear gene that is involved in regulating mitochondrial mRNA expression. Expression of mitochondrial genes may be under the control of other cytokines or hormones, and preliminary data show that other cytokines can have both positive and negative regulatory actions on mitochondrial gene expression. 3 Thyroxine and dexamethasone increase the levels of mitochondrial mRNAs (31), and thyroxine stimulates mitochondrial biogenesis leading to an increased number of organelles (32). TGF-β is localized in mitochondria of heart and liver cells (33). Regulation of mitochondrial activity may be a general phenomenon that occurs in both physiological and pathological conditions. A clear understanding of the mechanisms responsible for such regulation and its metabolic consequences is therefore an important goal.

tially no antiproliferative response to IFN. The absence of alterations in mitochondrial mRNA levels and electron transport activity agree with a link between the effect of IFN on mitochondrial activity and growth properties.

Alterations in mitochondrial metabolism might affect other responses to IFNs. Reduction of ATP levels could impede viral replicative mechanisms, but Richtsmeier and Grossberg (28) have reported that inhibitors of mitochondrial function reduce the antiviral response to IFN, suggesting that full mitochondrial function is needed to obtain the full response to type I IFNs. Activity of the antiviral enzyme 2’-5’-oligo(A) synthetase
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