Role of Interferon and 2',5'-Oligoadenylate Synthetase in Erythroid Differentiation of Friend Leukemia Cells

STUDIES WITH INTERFERON-SENSITIVE AND -RESISTANT VARIANTS*

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It has been suggested that the interferon (IFN)-induced 2',5'-oligoadenylate (2-5A) synthetase, which polymerizes ATP into a series of 2',5'-linked oligomers with the general formula pppA(2'p5'A)n, plays a general role in cell growth and terminal differentiation. For instance, an increase in 2-5A synthetase activity has been described during dimethyl sulfoxide (Me2SO)-induced erythroid differentiation of Friend leukemia cells (FLC).

2-5A synthetase has been measured in two Friend leukemia cell sublines by various techniques including a radioimmunoassay of its products which would detect 10^-14 mol of 2-5A cores. Although cells of both sublines fully differentiate (as measured by benzidine staining), only in one subline was there an increase in 2-5A synthetase activity upon treatment with Me2SO. Hexamethylenebisacetamide, another potent agent of differentiation in this system, did not increase 2-5A synthetase activity in either of these two sublines. An IFN-resistant FLC variant differentiated normally upon treatment with Me2SO or hexamethylenebisacetamide while it was nondicusable for 2-5A synthetase activity by exogenous IFN or by the inducers themselves. A similar situation has been observed with regard to the level of phosphorylation of the IFN-induced M, = 67,000 protein band. In addition, treatment of IFN-sensitive and resistant FLC sublines with mouse αIFN antiserum did not affect differentiation. Even though we have duplicated previous findings on the increase of 2-5A synthetase activity in Me2SO-induced FLC, the lack of any such increase with other inducers or other sublines indicates that there is no causal relationship between the enzyme activation and FLC differentiation.

Besides their antiviral activity, interferons(s) can serve as pleiotropic effector molecules in a variety of systems, including cells differentiating in vitro (Rossi et al., 1980, 1982). Extensive studies have revealed the major role played by two independent IFN'-induced enzymatic systems, namely the protein kinase and 2-5A synthetase pathways, both activated by double-stranded RNAs (for a review, see Lebleu and Content, 1982). The protein kinase phosphorylates the α subunit of initiation factor eIF-2 and a M, = 67,000 protein which may represent the kinase itself (for a review, see Sen, 1981). 2-5A synthetase polymerizes ATP into a series of 2',5'-linked oligomers with the general formula pppA(2'p5'A)n. These in turn bind specifically and activate an endoribonuclease (RNase L) which degrades RNAs (for a review, see Lengyel, 1981).

Since 2-5A synthetase activity varies extensively in different cell lines and within a given cell line according to growth conditions, a wider role for this pathway in the regulation of cell growth and differentiation has been proposed (Stark et al., 1979; Krishnan and Baglioni, 1980; Creasey et al., 1980; and others). In particular, increased levels of 2-5A synthetase activity (Kimchi, 1981) and the production of β-type IFN (Friedman-Einat et al., 1982) have been reported in growing and differentiating FLC exposed to Me2SO. It has also been reported that rabbit reticulocytes contain high levels of protein kinase and 2-5A synthetase (Farrell et al., 1977; Hovanessain and Kerr, 1978). Similarly, low doses of IFN enhance the expression of differentiation markers upon induction of FLC with Me2SO (Lieberman et al., 1975; Luftig et al., 1977; Dolei et al., 1980; Rossi et al., 1980).

In this report, we describe experiments carried out in this context on two FLC sublines and on an IFN-resistant variant isolated from one of them (Affabris et al., 1982). This variant does not exhibit any 2-5A synthetase activity even when exposed to 10,000 units/ml of αIFN (Affabris et al., 1983).

EXPERIMENTAL PROCEDURES

Materials—[2,8-3H]Adenosine 5'-triphosphate, tetrasodium salt (25-40 Ci/mmol) was obtained from New England Nuclear and adenosine 5'-[3-32P]triphosphate, triethylammonium salt (3000 Ci/mmol) was from the Radiocal polarisation 13, Amersham, U. K. Poly(rI)-poly(rC) was from P-L Biochemicals. Benzidine dihydrochloride was from Ciba. Me2SO and polystyrene glycol 6000 were from Merck. HMBA was a generous gift of C. Delfini, Istituto Superiore di Sanità, Rome, Italy. Bacterial alkaline phosphatase (EC 3.1.3.1) type IIIR was purchased from Sigma. All other chemicals and solvents were of reagent grade.

Cells—Two sublines, both derived from the 745A clone and ob-

* The abbreviations used are: IFN, interferon; Me2SO, dimethyl sulfoxide; FLC, Friend leukemia cells; HMBA, hexamethylenebisacetamide; NBS, newborn bovine serum; MEM, minimal essential medium; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid. 2-5A designates a series of oligonucleotides of the general formula pppA(2'p5'A)n, produced by the IFN-induced 2-5A synthetase.
tained from C. Friend, Mount Sinai Medical Center, New York, were independently passed for several years in the laboratories of L. Harel (Institut de Recherches Scientifiques sur le Cancer (IRSC), Villejuif) or G. B. Rossi. They will be referred hereafter as 745A\textsubscript{R} and 745A\textsubscript{S}, respectively. Cells of these sublines and of 745A\textsubscript{C1}, an IFN-resistant subline derived from 745A\textsubscript{R} (Affabris et al., 1983), were grown in MEM supplemented with 10% (v/v) NBS. L929 cells were grown in MEM supplemented with 5% (v/v) fetal calf serum.

Vesicular stomatitis virus (Indiana strain) stocks, obtained by infecting L929 cell monolayers with low multiplicity of infection (0.01–0.1 plaque-forming unit/cell) were titrated by plaque assay on the same cells. Titers ranged between 10\textsuperscript{6} and 10\textsuperscript{7} plaque-forming units/ml. Newcastle Disease virus, strain F, stocks were obtained by infecting 10–11-day-old embryonated eggs in the allantoic cavity. This standard preparation are reported in Research Reagents Note No. 15 (World Health Organization Standard, 1979).

Interferon—Mouse aIFN was prepared on C243-3 cells according to Cachard and De Maeyer-Guignard (1981). Briefly, confluent monolayers of C243-3 cells were infected with MEM containing 0.5% (v/v) NBS, and 5 mM Na\textsubscript{2}EDTA. Cells were then infected with Newcastle disease virus (10\textsuperscript{5} hemagglutinating units/ml) and reincubated with MEM containing 0.5% (v/v) NBS, and 5 mM Na\textsubscript{2}EDTA. After 1 h of adsorption, the monolayers were washed with isotonic buffered saline and reincubated with MEM containing 5% (v/v) fetal calf serum. Specific activities of IFN are given throughout this paper in laboratory units, i.e. the amount of IFN reducing by 50% plaque production by vesicular stomatitis virus, evaluated by the trypan blue dye exclusion method, never exceeded 40% plaque reduction.

Assay of Protein Kinase Activity—Extracts (postmitochondrial supernatant fractions) were prepared at 4°C from packed cells lysed into 1.5 volumes of homogenization buffer (10 mM Tris-HCl, pH 7.5, 7 mM \(\beta\)-mercaptoethanol, 10 mM KCl, 1.5 mM Mg(OAc)\textsubscript{2}, 0.5% (v/v) Nonidet P-40). The homogenate was brought to 3 mM Tris-HCl, pH 7.5, 90 mM KCl, 3.5 mM Mg(OAc)\textsubscript{2}, and 7 mM \(\beta\)-mercaptoethanol, and centrifuged at 10,000 \(\times\) g for 10 min. The supernatant fluid was either assayed immediately or stored in aliquots in liquid nitrogen. 5 \(\mu\)l of cell extract were incubated for 15 min at 37°C in 10 mM HEPES buffer, pH 7.6, 90 mM KCl, 10 mM Mg(OAc)\textsubscript{2}, 1 mM dithiothreitol, 100 \(\mu\)M ATP, 20% (v/v) glycerol, 2 \(\mu\)l of (\(\gamma\)\textsuperscript{32}P)ATP with or without poly(rI)-poly(rC) (1 \(\mu\)g/ml), in a final volume of 25 \(\mu\)l. After incubation, 2 volumes of electrophoresis sample buffer (125 mM Tris-HCl, pH 6.8, 100 mM \(\beta\)-mercaptoethanol, 10% (v/v) glycerol, 2% (v/v) Na dodecyl sulfate, 0.005% (v/v) bromphenol blue) were added to the kinase assay mix which was then heated to 55°C for 15 min and subjected to electrophoresis on 9% polyacrylamide slab gels containing 0.5% (w/v) Na dodecyl sulfate (Laemmli, 1970). The phosphorylated proteins were detected by autoradiography.

**RESULTS**

**2-5A Synthetase Activity in Several Growing and Differentiating FLC Sublines Treated with Me\textsubscript{2}SO—**Cells of two FLC sublines (745A\textsubscript{R} and 745A\textsubscript{S}) and of one IFN-resistant variant (745A\textsubscript{R}C1) were seeded at 10\textsuperscript{4} cells/ml in medium supplemented with Me\textsubscript{2}SO and were grown for 6 days under stationary conditions. As shown in Fig. 1A, the three growth curves were similar. Under these conditions, erythroid differentiation, as measured by hemoglobin-containing (benzidine-positive) cells, attained nearly 100% in all three lines (Fig. 1B).

In accordance with published data (Kimchi, 1981), 2-5A synthetase activity increased in parallel with the accumulation of benzidine-positive cells in the 745A\textsubscript{R} subline. On the contrary, neither the wild type 745A\textsubscript{S} subline nor the IFN-resistant variant derived therefrom, exhibited any detectable enzyme activity (Fig. 1C). It was verified that 745A\textsubscript{R} cells responded to exogenous mouse aIFN with the expected elevation in 2-5A synthetase activity (as shown by Affabris et al., 1983) while 745A\textsubscript{R}C1 cells did not respond to such treatment (data not shown), as previously described (Affabris et al., 1983).

**FIG. 1.** Cell growth, erythroid differentiation, and 2-5A synthetase activity of IFN-sensitive and -resistant FLC sublines. Cells were seeded at 10\textsuperscript{4} cells/ml in the presence of 1.5% (v/v) Me\textsubscript{2}SO. Cell growth (A), percentage of benzidine-positive cells (B), and 2-5A synthetase activity (C) were evaluated daily as described under "Experimental Procedures" for 745A\textsubscript{R} (C), 745A\textsubscript{S} (D), and 745A\textsubscript{R}C1 (E) sublines. The dotted lines in B refer to the differentiation of cell cultures in the absence of the inducer.
As 2-5A synthetase levels have been reported to be related to growth conditions (Krishnan and Baglioni, 1980; Creasey et al., 1980), two additional protocols were also followed. 745A\textsubscript{R} cells seeded at 5 \times 10^5/ml in Me\textsubscript{2}SO-rich medium were counted daily and diluted in Me\textsubscript{2}SO-containing medium to the initial concentration for 8 days. Alternatively, cells of the same subline were seeded at 10^5/ml in the same medium, counted 3 days later (when cell saturation density had not yet been attained), diluted to 2 \times 10^5/ml in Me\textsubscript{2}SO-rich medium, and grown for 8 days, essentially as described by Friedman-Einat et al. (1982). Although the percentage of benzidine-positive cells attained nearly 100% in all these conditions, no increase in 2-5A synthetase activity could be detected (data not shown). Likewise, no increase in 2-5A synthetase was observed when cells were diluted in Me\textsubscript{2}SO-free medium (data not shown).

Since even very low levels of 2-5A synthetase activity could suffice to activate RNase L and therefore be biologically meaningful, these negative data have been re-assessed with a radioimmunological assay of 2-5A cores (Cailla et al., 1982a). The cell-free products of 2-5A synthetase were dephosphorylated with alkaline phosphatase and quantified using monoclonal antibodies specifically detecting as low as 1 mol of 2-5A cores (Cailla et al., 1982b). Fig. 2 shows the linear conversion of ATP into 2-5A expected for an enzymatic assay. The cell-free products of 2-5A synthetase were dephosphorylated with bacterial alkaline phosphatase and processed for radioimmunosenasay as described in the text. 2-5A concentrations are expressed in nanomoles of 2-5A/10\textsuperscript{6} cells. * shows the data obtained for untreated 745A\textsubscript{R} cells on an expanded scale.

**Fig. 2. Radioimmunological determination of 2-5A synthetase activity in cell extracts of FLC.** Extracts were prepared from untreated (C) or IFN-treated (D) (200 units/ml) 745A\textsubscript{R} cells and assayed for 2-5A synthetase activity as described under "Experimental Procedures." 2-5A oligonucleotides were dephosphorylated with bacterial alkaline phosphatase and processed for radioimmunosenasay as described in the text. 2-5A concentrations are expressed in nanomoles of 2-5A/10^6 cells. * shows the data obtained for untreated 745A\textsubscript{R} cells on an expanded scale.

### Table I

**Radioimmunological analysis of 2-5A synthetase activity in FLC extracts**

| Subline | Inducer | B\textsuperscript{+} cells | 2-5A synthetase activity | % |
|---------|---------|-----------------------------|--------------------------|---|
| 745A\textsubscript{R} | Me\textsubscript{2}SO, 4 days | 78 | 0.118 |
| 745A\textsubscript{R} | Me\textsubscript{2}SO, 6 days | 96 | 0.132 |
| 745A\textsubscript{R} | HMBA, 4 days | 74 | 0.112 |
| 745A\textsubscript{R} | HMBA, 6 days | 99 | 0.108 |

### Table II

**2-5A synthetase activity in several FLC sublines treated with hexamethylenebisacetamide**

Cells were seeded at 10^5/ml with or without 5 mM HMBA and grown in stationary conditions. B\textsuperscript{+} values were determined as described under "Experimental Procedures." 2-5A synthetase activities, measured with the conventional assay of Minks et al. (1979), were expressed in nanomoles of ATP transformed/h/mg of protein and those measured with the radioimmunological assay were expressed in nanomoles of ATP transformed/10^6 cells (values in parentheses), as described in the text.

| FLC subline | Inducer | B\textsuperscript{+} cells | 2-5A synthetase activity | % |
|-------------|---------|-----------------------------|--------------------------|---|
| 745A\textsubscript{R} | HMBA, 4 days | 76 | <1 (0.134) |
| 745A\textsubscript{R} | HMBA, 6 days | 98 | <1 (0.054) |
| 745A\textsubscript{R} | HMBA, 4 days | 74 | <1 (0.12) |
| 745A\textsubscript{R} | HMBA, 6 days | 99 | <1 (0.068) |
| 745A\textsubscript{H} | HMBA, 4 days | 49 | <1 |
| 745A\textsubscript{H} | HMBA, 6 days | 100 | <1 |
| IFN-HMBA | ND | ND | 215 |
| IFN-HMBA | ND | ND | 221 |

*ND, not done.*

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1 S. Scoarne, P. Milhaud, and B. Lebleu, unpublished observations.

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25A Synthetase and Differentiation in Friend Cells

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2-5A Synthetase in FLC Sublines Treated with Hexamethylenbisacetamide—Since Me\textsubscript{2}SO has been shown to increase 2-5A synthetase activity in several cell lines (Besançon et al., 1981), the effects of HMBA, another potent inducer of differentiation in the FLC system (Reuben et al., 1980), have been investigated. As shown in Table II, nearly 100% of either 745A\textsubscript{H} or 745A\textsubscript{R} cells became benzidine-positive after 6 days of exposure to 5 mM HMBA. 2-5A synthetase activity remained undetectable in fully differentiated 745A\textsubscript{R} and 745A\textsubscript{R} 1C11 cells after HMBA treatment, thus confirming the data obtained with Me\textsubscript{2}SO for these two sublines. Surprisingly, HMBA did not stimulate 2-5A synthetase activity in 745A\textsubscript{H} cells (Table II), at variance with the data obtained with Me\textsubscript{2}SO (see above). HMBA even diminished the basal level of 2-5A synthetase activity which could be measured with the more sensitive radioimmunosenasay of 2-5A products (Table II).
2-5A Synthetase and Differentiation in Friend Cells

FLC—If IFN were released during FLC differentiation, as recently proposed (Friedman-Einat et al., 1982), it should increase the double-stranded RNA-activated protein kinase activity. Extracts were thus prepared from FLC induced to differentiate with either HMBA or Me₂SO, for increasing periods of time and incubate with γ-²³P-labeled ATP with or without double-stranded RNA. None of these conditions led to an increased level of phosphorylation of the M₉ = 67,000 protein band in 745AR and 745AR 1C11 sublines (Fig. 3) and in 745AH up to day 6 (data not shown). On the contrary, extracts prepared from exogenous IFN-treated FLC did exhibit the characteristic double-stranded RNA-dependent increase of the M₉ = 67,000 band phosphorylation, although less pronounced than for IFN-treated L929 cells taken as a positive reference (Fig. 3).

Effects of IFN Antiserum on FLC Erythroid Differentiation—Neutralization of IFN effects with a specific antiserum should provide an alternative approach to the elucidation of the role of IFN-induced enzymes in erythroid cell differentiation, if indeed any increase in their activity resulted from IFN release. FLC were treated with an antiserum raised against an unfractionated preparation of mouse α₂IFN at doses shown in preliminary experiments to completely inhibit exogenous IFN-induced 2-5A synthetase activity. As described in Fig. 4, such a treatment did not significantly affect FLC growth (A) or differentiation induced by Me₂SO as measured by the increase in benzidine-positive cells (B) or by spectrophotometric determination of hemoglobin content (C). IFN was included in parallel experiments as a control of antiserum efficacy, as described in Fig. 4.

DISCUSSION

The terminal differentiation of one FLC subline is accompanied by an increase of the IFN-induced 2-5A synthetase, as originally described by Kimchi (1981). However, the data presented in this paper do not support a general role of 2-5A synthetase induction in the differentiation of erythroid cells, as: 1) an increase in 2-5A synthetase activity following Me₂SO treatment is not observed in a closely related but independently passaged FLC subline; and 2) HMBA does not modulate 2-5A synthetase activity even in the FLC subline (745AH) which shows an increase of 2-5A synthetase activity following Me₂SO treatment.

These data are in keeping with the absence of any detectable increase in 2-5A synthetase activity in five of five of the IFN-resistant variants isolated in this laboratory (Affabris et al., 1983) while all of them respond to inducers of differentiation.
indistinguishably from their wild type parent.

The observed differences in the ability of Me₂SO and HMBA to increase 2-5A synthetase activity in at least one FLC subline is not surprising. It has been shown that differentiation inducers such as Me₂SO or Na butyrate increase 2-5A synthetase activity in several unrelated lines such as C243 aurine fibroblasts (Besançon et al., 1981) or HeLa cells, which are not known to express markers specific to a given differentiation lineage.

Since subnanomolar amounts of 2-5A suffice to activate RNase L (Lengyl, 1981), conventional assays for measuring 2-5A synthetase activity might not have been sensitive enough to detect low amounts of 2-5A products still of possible biological significance. Indeed, a recently developed sensitive radioimmunooassay of 2-5A products in the nuclei (Nilsen et al., 1982a) did allow us to measure previously undetectable basal levels of 2-5A synthetase activity in all three sublines. Yet, Me₂SO was unable to modulate these levels in 745AR and the IFN-resistant variant cells. We cannot exclude, however, a role of the 2-5A synthetase recently detected in the nuclei (Nilsen et al., 1982; St. Laurent et al., 1983) in the differentiation process of FLC, as experimental conditions conventionally used to assay 2-5A synthetase do not lead to a major disruption of the nuclei.

Likewise, a localized activation of the 2-5A system (as hypothesized by Nilsen and Baglioni, 1979) in the intact differentiating FLC could have escaped our detection and yet play a significant biological role.

2-5A synthetase induction could merely reflect the increased level of 2-5A synthetase activity accompanying mouse myeloid leukemia cell differentiation without preventing differentiation itself (Sokawa et al., 1981). This does not exclude, however, a role of IFN and of the 2-5A system in the regulation of growth and differentiation in other systems such as rat liver regenerating after partial hepatectomy (Kimchi, 1981).

Considering the presence of a 2-5A synthetase activity reported in mammalian reticulocytes (Hovanessian and Kerr, 1978) and the data reported in this paper, we might hypothesize that any such increase takes place very late in the process of erythroid cell differentiation, e.g. at a stage preceding closely the extrusion of the nucleus. Differences in FLC sublines would then easily explain why only some of them (see the data reported here for 745AR and those reported by Kimchi (1981)) do reach this stage while others do not (see data reported here for 745AR and for HMBA-induced 745AR). Whatever the case, the 2-5A systems per se (i.e. independently from exogenous IFN addition) would not play any role either in the commitment of FLC to terminal differentiation or in the hemoglobinization process which is fully expressed in this in vitro system (Cioè et al., 1978).

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