Following treatment of mouse erythroleukemia (MEL) cells with dimethyl sulfoxide and other typical erythroid inducing agents, the profile of cellular phosphotyrosine-containing proteins was drastically altered. We found that the level of almost all of the phosphotyrosine-containing proteins was either decreased or disappeared at a very early stage of differentiation. Addition of sodium orthovanadate (Na$_3$VO$_4$), a specific inhibitor of phosphotyrosine phosphatases, prevented the alteration as well as erythroid differentiation. Mutant MEL cells, which are resistant to differentiation by dimethyl sulfoxide, were apparently insensitive to the alteration. These results indicate that dephosphorylation of phosphotyrosine residues in cellular proteins is coupled with a reaction(s) which is responsible for triggering differentiation of MEL cells.

Mouse erythroleukemia (MEL) cells differentiate into erythroid cells in vitro to response to a number of compounds, which include dimethyl sulfoxide (Me$_2$SO) (Friend et al., 1978), hexamethylenedisacetamide (HMBA) (Reuben et al., 1976), sodium butyrate (Leder and Leder, 1975; Takahashi et al., 1975), trichostatic acid (Trichostatin A) (Yoshida et al., 1987), and others (Marks and Riskind, 1978). Although these compounds are structurally unrelated, they are all very effective in inducing differentiation. One of the attractive speculations of how these compounds with a wide spectrum of structures and presumably different biological functions induce differentiation is that the molecular cascade leading to erythroid differentiation is quite diversified at the initial stage of differentiation but eventually converges to a common and critical step which is responsible for the cellular commitment to differentiation. In order to identify the molecular nature of such a step, we searched for compounds with known biological activities, which can act as inducers for erythroid differentiation. Recently, we found that a series of inhibitors of protein tyrosine kinases are very effective inducers for erythroid differentiation of MEL cells (Kondo et al., 1989, 1991). Among them, herbimycin A induced not only erythroid differentiation of MEL cells but also embryonal differentiation of mouse embryonal carcinoma (F9) cells (Kondo et al., 1989). Another tyrosine kinase inhibitor, genistein, induced MEL cell differentiation by itself at relatively high concentrations, but at lower concentrations it exhibited inducing activity only when DNA damaging agents such as mitomycin C or topoisomerase inhibitors like camptothecin or VM26 were also present in the medium (Watanabe et al., 1989, 1992). The synergistic effect of tyrosine kinase inhibitors with DNA damaging agents or topoisomerase inhibitors was confirmed by finding a similar erythroid-inducing activity in other tyrosine kinase inhibitors, synthetic analogues of phosphotyrosine such as ST638 and methyl-2,5-dihydroxycinnamate (Watanabe et al., 1989). No such synergistic erythroid-inducing activities were detected with serine/threonine kinase inhibitors (Watanabe et al., 1991, 1992).

In order to further investigate the possible role of protein phosphorylation and dephosphorylation of tyrosine residues in erythroid differentiation, we examined whether the pattern of cellular phosphotyrosine-containing proteins is altered during in vitro differentiation. Here we report that most cellular phosphotyrosine-containing proteins were either decreased or had disappeared at a very early stage of erythroid differentiation. The possible biological significance of dephosphorylation of phosphotyrosine residues of cellular proteins is discussed with respect to the mechanism of erythroid differentiation of MEL cells.

### MATERIALS AND METHODS

Sodium orthovanadate (Na$_3$VO$_4$) was purchased from Aldrich. HMBA was a gift from Dr. T. Yamauchi (Bell Laboratories). Okadaic acid and Trichostatin A were provided by Drs. Y. Hashimoto (University of Tokyo), and M. Yoshida and T. Beppu (University of Tokyo), respectively. These reagents were stocked at the following concentrations in solvents (in parentheses) and appropriately diluted with H$_2$O when used: HMBA, 1 M (H$_2$O); sodium butyrate, 100 mM (H$_2$O); okadaic acid, 2 mM (ethanol); Trichostatin A, 1 mg/ml (ethanol); and Na$_3$VO$_4$, 10 mM (medium). Minimal essential medium was purchased from Nissui Seiyaku. Fetal calf serum was obtained from United Biotechnologies (Tokyo). Mouse monoclonal anti-phosphotyrosine antibody (PY20, lot 32188) and sheep anti-mouse IgG horseradish peroxidase-conjugated antibody were purchased from ICN and Amersham Corp., respectively.

### Cells and Cell Culture—MEL (Friend) cells (745A) were supplied by Dr. M. Terada (National Cancer Center Institute). Differentiation-resistant MEL cells (DMSO'-1, DMSO'-2, DMSO'-3, and DMSO'-4) were isolated in this laboratory after treating the cells with N-nitrosoguanidine. Spontaneous revertants which restored the capacity of differentiation designated as DMSO'-2, DMSO'-3, and DMSO'-4 were isolated from DMSO'-2, DMSO'-3, and DMSO'-4, respectively. The cells were cultured at 37 °C in a CO$_2$ (5%) incubator in minimal essential medium supplemented with 12% (v/v) fetal calf serum.

### Assay of Hemoglobin—Cells which accumulated hemoglobin were stained by benzidine as described by Orkin et al. (1978). Detection of Phosphotyrosine-containing Proteins—Cells (~2 x 10$^6$) were washed with phosphate-buffered saline containing 1 mM Na$_3$VO$_4$ and 5 mM EDTA, then lysed by incubating in 100 µl of TNEP buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 4 mM EDTA, 2 mM Na$_3$VO$_4$, 10 mM sodium pyrophosphate, 10 mM NaF, 1% (v/v) Nonidet P-40,
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1% (w/v) SDS, and 1 trypsin inhibitor unit/ml of aprotinin) for 20 min at 0 °C. After centrifuging the lysate (15,000 rpm for 20 min), the supernatant was mixed with SDS-PAGE sample buffer (final concentration: 63 mM Tris-HCl, pH 6.8, 2.3% (w/v) SDS, 1% (v/v) β-mercaptoethanol, and 10% (v/v) glycerol) and boiled for 5 min. The samples (50 μg of protein) were separated by SDS-PAGE (7.5%, w/v, polyacrylamide, 15 mA electric current, 1 h) using SDS-PAGE running buffer (25 mM Tris base, 19 mM glycine, and 0.1% (w/v) SDS). After electrophoresis, proteins were electrotransferred to a polyvinylidene difluoride membrane (Bio-Rad) as described below. The gel was layered on top of a polyvinylidene difluoride membrane which had been placed on two layers of Whatman 3MM papers. Each 3MM paper had been soaked in different buffers; the top in buffer B and the bottom in Buffer A, respectively (see below). Another 3MM paper, presoaked in buffer C (see below), was placed on top of the gel, and electrotransfer was performed with electric current running from the bottom (+) to the top (−) of the layers. The compositions of the buffers used are as follows: buffer A, 300 mM Tris-HCl (pH 10.4), 20% (v/v) methanol and 0.02% (w/v) SDS, buffer B, 25 mM Tris-HCl (pH 10.4), 20% (v/v) methanol, and 0.02% (w/v) SDS; and buffer C, 25 mM Tris-HCl (pH 9.4), 20% (v/v) methanol, 0.02% (w/v) SDS, and 40 mM amino-n-caproic acid. Phosphotyrosine-containing proteins were detected by mouse monoclonal anti-phosphotyrosine antibody (0.2 μg/ml) and sheep anti-mouse IgG horseradish peroxidase-conjugated antibody, followed by enhanced chemiluminescence detection (Amersham Corp.). Control experiments indicated that the antibody reacted specifically with phosphotyrosine-containing proteins under the condition described above (data not shown).

RESULTS

In order to explore the possible role of protein phosphorylation (and dephosphorylation) of tyrosine residues in in vitro differentiation, we first investigated whether the level of cellular phosphotyrosine-containing proteins is altered during erythroid differentiation. For this, MEL cells were incubated in the presence of Me2SO, a typical erythroid-inducing agent, and cell-free extracts were prepared at different time intervals up to 120 h of incubation at which the differentiation was virtually completed. The extracts were then electrophoresed (SDS-PAGE) and Western-blotted using an anti-phosphotyrosine antibody. As seen in Fig. 1, during the first several hours of incubation with Me2SO, the profile of cellular phosphotyrosine-containing proteins was dramatically altered (mostly decreased) and remained at that level for up to 120 h of incubation. We estimated that approximately 80% of the cellular phosphotyrosine-containing proteins become non-reactive to the anti-phosphotyrosine antibody. The alteration of the profile, most significantly the decrease or disappearance of most of the phosphotyrosine-containing proteins, appeared to precede the cellular commitment to differentiation which occurs between 24 and 36 h after exposure of the cells to the inducing agent under the conditions used here. Similar alterations of the profile of phosphotyrosine-containing proteins were also observed following treatment of the cells with a variety of erythroid-inducing agents which included HMBA, sodium butyrate, Trichostatin A, and genistein. These compounds also induce erythroid differentiation quite effectively despite their different molecular structures and presumably different biological functions (Fried et al., 1978; Leder and Leder, 1975; Marks and Rifkind, 1978; Reuben et al., 1976; Takahashi et al., 1975; Yoshida et al., 1987). For example, whereas Trichostatin A is a compound which affects acetylation of nuclear proteins (Yoshida et al., 1990), genistein inhibits protein tyrosine kinases as well as topoisomerase II (Akiyama et al., 1987; Markovits et al., 1988; Okura et al., 1988). As seen in Fig. 2, all of these compounds altered the level of phosphotyrosine-containing proteins in essentially the same manner as observed in the cells incubated with Me2SO. Among major phosphotyrosine-containing proteins, we noticed that proteins with approximate molecular masses of 110, 105, 74, 58, 48, and 45 kDa were made to disappear or were greatly decreased by these inducing agents (indicated by arrowheads). These suggest that the effect of these inducing agents on the pattern of phosphotyrosine-containing proteins was associated with erythroid differentiation.

We examined the relationship between the alteration of the profile of phosphotyrosine-containing proteins and the extent of erythroid differentiation in the presence of various concentrations of each inducing agent. We saw in Fig. 3, with Me2SO, sodium butyrate, or HMBA, the profile started to change at the drug concentrations which became effective in inducing erythroid differentiation. These results further implicated a relationship, though a causal one, between the change in the pattern of cellular phosphotyrosine-containing proteins and the induction of erythroid differentiation.

In order to further investigate the phenomenon, the effect of Na2VO4 on erythroid differentiation as well as on the Me2SO-induced alteration of the pattern of phosphotyrosine-containing proteins was examined. Na2VO4 is an inhibitor of protein phosphatases specific to phosphotyrosine, but not of serine/threonine protein phosphatases (Leis and Kaplan, 1989; Okura et al., 1988). As seen in Fig. 1, the approximate molecular masses of these proteins are 110, 105, 74, 58, 45, and 45 kDa, respectively (from the top). Positions of molecular mass markers are shown on the left side of the figure.

Fig. 1. Profile of cellular phosphotyrosine-containing proteins during erythroid differentiation. MEL (745A) cells were incubated in the presence of Me2SO (280 mM). At the time (h) indicated on the figure, samples were withdrawn and cell-free extracts were prepared. After SDS-PAGE, they (50 μg of protein each) were Western blotted using anti-phosphotyrosine antibody as described under "Materials and Methods." Positions of molecular mass markers are shown on the left side of the figure.

Fig. 2. Alterations of the pattern of cellular phosphotyrosine-containing proteins by erythroid-inducing agents. MEL (745A) cells were incubated for 24 h in the absence (control) or presence of either Me2SO (DMSO, 280 mM), HMBA (5 mM), sodium butyrate (Na-butyrate, 1 mM), Trichostatin A (TSA, 50 ng/ml), or genistein (20 μg/ml). Cell-free extracts were prepared and, after SDS-PAGE, they (50 μg of protein each) were Western-blotted using anti-phosphotyrosine antibody as described under "Materials and Methods." Positions of molecular mass markers are shown on the left side of the figure.
Yj, sodium butyrate and HMBA (C). MEL (745A) cells were incubated for 24 h in the presence of various concentrations of Me2SO, HMBA, and sodium butyrate. Cell-free extracts were prepared and, after SDS-PAGE, they were Western-blotted using anti-phosphotyrosine antibody as described under "Materials and Methods." A: lane 1, untreated (control) cells; lane 2, Me2SO (77.8 mM); lane 3, Me2SO (155.6 mM); lane 4, Me2SO (235 mM); lane 5, Me2SO (280 mM); B: lane 1, untreated (control) cells; lane 2, sodium butyrate (0.1 mM); lane 3, sodium butyrate (0.5 mM); lane 4, sodium butyrate (1 mM). C: lane 1, untreated (control) cells; lane 2, HMBA (0.5 mM); lane 3, HMBA (1 mM); lane 4, HMBA (2.5 mM); lane 5, HMBA (5 mM). Erythroid differentiation assayed by the appearance of B' cells (%) under each condition is shown at the bottom of each lane. Positions of molecular mass markers are shown on the left side of the figure.

Fig. 3. Profile of cellular phosphotyrosine-containing proteins in the presence of various concentrations of Me2SO (A), sodium butyrate (B), and HMBA (C). MEL (745A) cells were incubated for 24 h in the presence of various concentrations of Me2SO, HMBA, and sodium butyrate. Cell-free extracts were prepared and, after SDS-PAGE, they were Western-blotted using anti-phosphotyrosine antibody as described under "Materials and Methods." A: lane 1, untreated (control) cells; lane 2, Me2SO (77.8 mM); lane 3, Me2SO (155.6 mM); lane 4, Me2SO (235 mM); lane 5, Me2SO (280 mM); B: lane 1, untreated (control) cells; lane 2, sodium butyrate (0.1 mM); lane 3, sodium butyrate (0.5 mM); lane 4, sodium butyrate (1 mM); C: lane 1, untreated (control) cells; lane 2, HMBA (0.5 mM); lane 3, HMBA (1 mM); lane 4, HMBA (2.5 mM); lane 5, HMBA (5 mM). Erythroid differentiation assayed by the appearance of B' cells (%) under each condition is shown at the bottom of each lane. Positions of molecular mass markers are shown on the left side of the figure.

Fig. 4. Effect of Na3VO4 and okadaic acid on the level of cellular phosphotyrosine-containing proteins. MEL (745A) cells were incubated for 24 h with either Me2SO (DMSO, 280 mM), Me2SO (280 mM) plus okadaic acid (10 mM), Me2SO (280 mM) plus Na3VO4 (50 μM), or Na3VO4 (50 μM). Cell-free extracts were prepared and, after SDS-PAGE, they were Western-blotted using anti-phosphotyrosine antibody as described under "Materials and Methods." A: lane 1, untreated (control) cells; lane 2, DMSO (280 mM); lane 3, DMSO plus okadaic acid (10 mM); lane 4, DMSO plus Na3VO4 (50 μM); lane 5, Na3VO4 (50 μM). Erythroid differentiation assayed by the appearance of B' cells (%) under each condition is shown at the bottom of each lane. Positions of molecular mass markers are shown on the left side of the figure.

We also investigated the profile of phosphotyrosine-containing proteins in several MEL cell lines which are resistant to differentiation. For this, we mutagenized MEL cells, and four mutant clones which were resistant to differentiation by Me2SO were independently isolated. The extent of erythroid differentiation (assayed by the appearance of B' cells) of the four clones (DMSO'-1, DMSO'-2, DMSO'-3, and DMSO'-4) after incubation with Me2SO for 120 h was all less than 0.1% as opposed to 80–90% observed with the parental clone (745A) (data not shown). These mutant clones were incubated in the presence or absence of Me2SO, and cell-free extracts, prepared after 24 h of incubation, were Western-blotted as described above. The results are shown in Fig. 6A. As seen in the figure, the profiles of phosphotyrosine-containing proteins of these clones after incubation with Me2SO were considerably different from that of the parental clone. It was quite clear that while these mutant cells exhibited profiles very similar to those of the parental cells under normal culture conditions without Me2SO, after incubation with Me2SO, all of these mutant cells either exhibited little alteration of phosphotyrosine-containing proteins (DMSO'-1) or they exhibited a decrease or disappearance of only a limited number of specific phosphotyrosine-containing proteins (DMSO'-2, DMSO'-3, DMSO'-4).

Fig. 5. Effect of Na3VO4 and okadaic acid on erythroid differentiation induced by Me2SO. MEL (745A) cells were incubated in the presence of Na3VO4 or okadaic acid for 2 days and followed by a 3-day incubation in their absence. Erythroid differentiation was assayed by counting the cells (B' cells) which had accumulated hemoglobin as described by Orkin et al. (1978). A, Me2SO (280 mM) plus Na3VO4 treatment; B, Me2SO (280 mM) plus okadaic acid treatment. Note that okadaic acid concentrations are shown on the logarithmic scale.

1982; Swarup et al., 1982). We first examined whether Na3VO4 affects the Me2SO-induced alteration of the profile of phosphotyrosine-containing proteins. As shown in Fig. 4, in the presence of Na3VO4 (50 μM) no decrease or disappearance of these proteins was observed, Na3VO4 apparently nullifying the effect of Me2SO. As seen in the figure, Na3VO4 even increased the level of most of the phosphotyrosine-containing proteins in the Me2SO-treated cells. No such effect was observed with okadaic acid, which is a specific inhibitor of serine/threonine protein phosphatases I and 2A (Bialojan and Takai, 1988; Haystead et al., 1989; Suganuma et al., 1988) (Fig. 4). The effect of Na3VO4, suggested that the decrease or loss of reactivity of most of the phosphotyrosine-containing proteins to a phosphotyrosine-specific antibody was not due to protein degradation but to dephosphorylation of the phosphotyrosine residues of these proteins by tyrosine protein phosphatases. Furthermore, the increase of the level of most of the phosphotyrosine-containing proteins by Na3VO4 even in the presence of Me2SO (Fig. 4) suggested that phosphatase moieties at tyrosine residues of cellular phosphotyrosine-containing proteins are rapidly being turned over under the conditions used here.

We found that Na3VO4 inhibited Me2SO-induced erythroid differentiation at the same concentration (50 μM) which inhibited the alteration of phosphotyrosine-containing protein (Fig. 5A). Na3VO4 also inhibited HMBA-induced-erythroid differentiation (data not shown). Addition of Na3VO4 after the cellular commitment to differentiation (48 h incubation with Me2SO) did not prevent the Me2SO-induced differentiation (data not shown). No such inhibitory activity was observed with okadaic acid (Fig. 5B). These results suggest that blocking dephosphorylation of tyrosine residues leads to the inhibition of erythroid differentiation, provided that protein tyrosine phosphatases are the only intracellular target of Na3VO4. Taken together, it seems that either inhibition of phosphorylation or acceleration of dephosphorylation of the tyrosine residues of phosphotyrosine-containing proteins, or both, is closely associated with an early event(s) in erythroid differentiation.

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and DMSO⁻⁴). For example, protein(s) of about 80 kDa (indicated by an arrow) disappeared in three of the differentiation-resistant clones (DMSO⁻², DMSO⁻³, and DMSO⁻⁴) despite the fact that these clones had been isolated independently. Essentially no effect of further incubation (up to 120 h) with Me₂SO on the profile of phosphotyrosine-containing proteins was observed with these mutant cell lines (data not shown). The apparent insensitivity of these mutant cells to the alteration of the phosphotyrosine-containing protein pattern was lost when the cells restored the capacity to differentiate. We examined the profile of phosphotyrosine-containing proteins of revertants from the DMSO⁻ cells in which the capacity of erythroid differentiation had been restored. The results of the analysis of extracts from three spontaneously reverted MEL cells (DMSO⁻², DMSO⁻³, and DMSO⁻⁴), are shown in Fig. 6B. It is evident that as these cells regained the capacity of differentiation, they became sensitive to the Me₂SO-induced alteration of the pattern of phosphotyrosine-containing proteins. For example, proteins with approximate molecular masses of 110, 105, 74, 58, and 48 kDa now became sensitive to Me₂SO treatment in all the three revertants. These results further confirmed the relationship between the alteration of phosphotyrosine-containing proteins and erythroid differentiation.

**DISCUSSION**

In this paper, we showed that during in vitro erythroid differentiation in MEL cells induced by Me₂SO, the profile of cellular phosphotyrosine-containing proteins was drastically altered. Most of the phosphotyrosine-containing proteins became non-reactive to an antibody against phosphotyrosine, suggesting that phosphate moieties at tyrosine residues of these proteins was dephosphorylated. The alteration occurred at the very early stage of differentiation and was observed during MEL cell differentiation induced not only by Me₂SO but also by a variety of erythroid-inducing agents. No alteration was observed in mutant cells resistant to differentiation. These results seem to have established a clone relationship between the pattern of the alteration of tyrosine-containing proteins and erythroid differentiation.

We also reported that a specific inhibitor of protein tyrosine phosphatases, Na₃VO₄, inhibited the differentiation itself as well as the alteration of tyrosine-containing proteins induced by Me₂SO. Thus, it is very likely that the alteration of the profile of cellular tyrosine-containing proteins observed at the early stage of MEL cell differentiation resulted from dephosphorylation of phosphotyrosine moieties by protein tyrosine phosphatases. Previously, we and others reported that inhibitors of protein tyrosine kinases such as herbimycin A, genistein, and others effectively induced differentiation of MEL and other cells (Honma et al., 1989; Kondo et al., 1989; Watanabe et al., 1989, 1991, 1992). The results presented here corroborate the suggestion that the differentiation-inducing activity of protein tyrosine kinase inhibitors was derived from the inhibition of phosphorylation of the tyrosine residues on specific proteins. Taken together, it is quite likely that protein dephosphorylation at tyrosine residues of probably specific proteins plays an important role in triggering MEL cell differentiation, although from the experiments presented here, we cannot deduce the exact cause of the dephosphorylation; it is either by inhibition of phosphorylation or stimulation of dephosphorylation at tyrosine residues.

The experimental results presented here do not necessarily contradict the possible involvement of protein kinase C in MEL cell differentiation (Melloni et al., 1989, 1990). In preliminary experiments, we found that phorbol 12-myristate 13-acetate, a specific inhibitor of MEL cell differentiation, had only a slight inhibitory effect on the decrease of phosphotyrosine-containing proteins after Me₂SO treatment. This may indicate that PMA inhibits MEL cell differentiation by acting at a step which is downstream of the dephosphorylation step of phosphotyrosine-containing proteins in the differentiation cascade. It is, however, also possible that phorbol 12-myristate 13-acetate does affect the dephosphorylation, but the effect is only at phosphotyrosine proteins which exist at a very low level. Such an effect would not have been recognized by the procedure employed here.

We found that the alteration profile of phosphotyrosine-containing proteins of mutant cells was quite different from those of the parental cells. Whereas most of the mutant cells exhibited the normal profile of phosphotyrosine-containing proteins, that after Me₂SO treatment was quite different from that of the parental cells, most of them being resistant to the alteration. However, the phosphotyrosine-containing protein profiles that emerged after the treatment of cells with Me₂SO were not all identical among the mutant cells. Whereas some of the mutant cells exhibited almost total resistance to the alteration, others exhibited alterations only with some of the
specific tyrosine-containing proteins (Fig. 6A). These suggest that alteration (dephosphorylation) of only a limited number of phosphotyrosine-containing proteins plays a critical role in triggering differentiation. Because of the complex profile of phosphotyrosine-containing proteins by the procedures used here, we did not pinpoint a putative substrate for a tyrosine phosphatase(s) which would likely be responsible for erythroid differentiation. Identification of the target protein(s) as well as the specific tyrosine protein phosphatase(s) involved in erythroid differentiation should be the next step in elucidating the role of protein dephosphorylation in erythroid differentiation.

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