We have recently reported that neolacto series gangliosides (NeuAc-nLc) are increased during granulocytic differentiation of human myelogenous leukemia cell line HL-60 cells induced by retinoic acid and that HL-60 cells are differentiated into mature granulocytes when the cells are cultivated with NeuAc-nLc (Nojiri, H., Kitagawa, S., Nakamura, M., Kiriti, K., Enomoto, Y., and Saito, M. (1988) J. Biol. Chem. 263, 7443–7446). In contrast to these wild-type HL-60 cells, HL-60 cells resistant to differentiation induction by retinoic acid showed a markedly decreased content of gangliosides, especially NeuAc-nLc, and did not show any increase in the content of gangliosides when cultivated with retinoic acid. Neutral glycosphingolipids, the precursors of gangliosides, were not accumulated in these resistant cells. When retinoic acid-resistant HL-60 cells were cultivated in the presence of NeuAc-nLc, the cells were found to be differentiated into mature granulocytes on morphological and functional criteria. The differentiation of cells was dependent on the concentration of gangliosides and was accompanied by inhibition of cell growth. Wild-type HL-60 cells differentiated by NeuAc-nLc showed the changes in ganglioside composition, which were similar to those in wild-type HL-60 cells differentiated by retinoic acid; among the gangliosides changed, 2 → 3 sialylparagloboside and 2 → 3 sialylparagloboside were increased. These findings suggest that the synthesis of particular NeuAc-nLc molecules is an important step for retinoic acid-induced granulocytic differentiation and this step could be bypassed or replaced by exogenous NeuAc-nLc, and (b) that the defective synthesis of particular NeuAc-nLc molecules is responsible for the failure of differentiation induction in retinoic acid-resistant HL-60 cells by retinoic acid.

We have recently reported that the particular ganglioside molecules play an important role in the regulation of the differentiation of human myelogenous leukemia cell line HL-60 cells (1–5). The ganglioside series ganglioside IP'NeuAc-LacCer (GMP) is increased during monocytic differentiation of HL-60 cells induced by phorbol 12-myristate 13-acetate (PMA). When HL-60 cells are cultivated in the presence of GMP, the cells are differentiated into monocytic cells (1–4). On the other hand, neolacto series gangliosides (NeuAc-nLc) are increased during granulocytic differentiation of HL-60 cells induced by retinoic acid or dimethyl sulfoxide. When HL-60 cells are cultivated in the presence of NeuAc-nLc, the cells are differentiated into granulocytic cells (1, 2, 5). These findings suggest that the appearance or accumulation of particular ganglioside molecules on the cell surface membrane plays an important role in the triggering of differentiation and the determination of differentiation direction in HL-60 cells.

In order to clarify further the role of gangliosides in differentiation induction, we analyzed in this paper the glycosphingolipids in HL-60 cells resistant to differentiation induction by retinoic acid. We found that (a) the content of gangliosides (sialic acid-containing glycosphingolipids), especially NeuAc-nLc, in retinoic acid-resistant HL-60 cells was markedly decreased as compared with that in parental wild-type HL-60 cells; (b) the content of gangliosides in retinoic acid-resistant HL-60 cells was not increased by cultivation with retinoic acid; (c) retinoic acid-resistant HL-60 cells were differentiated into mature granulocytes when the cells were cultivated in the presence of NeuAc-nLc; and (d) wild-type HL-60 cells differentiated by NeuAc-nLc showed changes in ganglioside composition that were similar to those in wild-type HL-60 cells differentiated by retinoic acid.

**MATERIALS AND METHODS**

**Cells and Cell Culture**—Human myelogenous leukemia cell line HL-60 cells were grown in a serum-free synthetic medium (DME/F-12) as described (4, 5). The retinoic acid-resistant HL-60 subline was selected by cultivating wild-type HL-60 cells in the presence of retinoic acid, the concentration of which was sequentially increased up to 1.0 μM as described previously (6, 7). Retinoic acid (1 μM) was always added to the culture medium for retinoic acid-resistant HL-60 cells unless otherwise indicated. For induction of the differentiation of HL-60 cells, cells were seeded at 2 × 10⁶ cells/ml and grown in the presence or absence of retinoic acid (Sigma) or NeuAc-nLc. The preparation of NeuAc-nLc used in the present experiments was a mixture of gangliosides isolated from peripheral blood granulocytes that were obtained from the patients with chronic myelogenous leukemia. The ganglioside preparation contained 96.5% NeuAc-nLc.

1. The nomenclature for glycosphingolipids follows the recommendations of the Nomenclature Committee of the International Union of Pure and Applied Chemistry (48).

2. The abbreviations used are: PMA, phorbol 12-myristate 13-acetate; O₂⁻, superoxide; fMLP, formylmethionylleucycophenylalanine; NeuAc-nLc, neolacto series gangliosides.
and 3.5% GM3 (5). The concentration of NeuAc-nLc was determined on the basis of lipid-bound sialic acid. Cell viability was determined by the erythrosin B dye exclusion test.

**Analysis of Gangliosides**—Gangliosides from the cells were prepared by chloroform/methanol extraction and DEAE-Sephadex chromatography and analyzed quantitatively by densitometric scanning on a high performance thin-layer chromatography plate (Merck, Darmstadt, Federal Republic of Germany) as described (1, 2, 5, 8). Lactosylceramide and 3.5% GM3 were analyzed by densitometric scanning on a high performance thin-layer chromatography plate as described (12). The hexose content of the neutral ganglioside fraction was measured by the phenol-sulfuric acid method (13).

**Determination of Cell Differentiation**—The morphological assessment of the cells was performed under a light and an electron microscope as described (4, 5). The activity of naphth AS-D chloroacetate esterase or α-naphthyl butyrate esterase was determined by the esterase double staining method (5). The phagocytic activity toward polystyrene latex particles and the nitro blue tetrazolium reduction for PMA and from cytochrome c were measured by the continuous assay was performed in a Hitachi 557 spectrophotometer (Ortho Diagnostic Systems, Inc., Westwood, MA) using the authorizations of the Nomenclature Committee of the International Union of Pure and Applied Chemistry (43).

### RESULTS

**Decreased Content of Gangliosides in Retinoic Acid-resistant HL-60 Cells**—The thin-layer chromatograms of gangliosides in wild-type and retinoic acid-resistant HL-60 cells are shown in Fig. 1, and the data are summarized in Table I. The total content of gangliosides of retinoic acid-resistant HL-60 cells was approximately one-sixth that of parental wild-type HL-60 cells. The content of GM3 was almost equivalent in both types of cells, whereas the content of NeuAc-nLc in retinoic acid-resistant HL-60 cells was markedly diminished as compared with that in wild-type HL-60 cells.

![Fig. 1. Thin-layer chromatograms of gangliosides (A) and neutral glycosphingolipids (B) in wild-type (lane a) and retinoic acid-resistant (lane b) HL-60 cells. The ganglioside fractions corresponding to 5 × 10⁶ cells and the neutral glycosphingolipid fractions equivalent to 20 μg of hexose were applied, respectively. A: 1, IV'NeuAc-nLcOse4Cer; 2, IV'NeuAc-nLcOse6Cer; 3, VII'NeuAc-nLcOse4Cer; 4, VII'NeuAc-nLcOse6Cer; 5, VII'NeuAc-nLcOse8Cer; 6, VII'NeuAc-nLcOse10Cer. B: 1, GalCer; 2, LacCer; 3, LcOseCer; 4, nLcOseCer.](image)

![Table I](image)

| Treated with | Wild-type HL-60 | Retinoic acid-resistant HL-60 |
|--------------|----------------|----------------------------|
| Control | NeuAc-nLc | Retinoic acid | Control | Retinoic acid |
| μg lipid-bound sialic acid/10⁶ cells | | | | |
| III'NeuAc-LacCer (GalCer) | 0.43 | 0.45 | 0.49 | 0.34 | 0.32 |
| IV'NeuAc-nLcOse4Cer | 1.04 | 1.37 | 1.26 | 0.04 | 0.03 |
| V'NeuAc-nLcOse6Cer | 0.63 | 0.09 | 0.23 | 0.05 | 0.05 |
| VI'NeuAc-nLcOse8Cer | 0.73 | 0.83 | 1.41 | 0.06 | 0.13 |
| VII'NeuAc-nLcOse10Cer | 0.02 | 0.02 | 0.02 | 0.02 | 0.03 |
| VII'NeuAc-nLcOse12Cer | 0.10 | 0.10 | 0.28 | <0.01 | <0.01 |
| VII'NeuAc-nLcOse14Cer | 0.12 | 0.16 | 0.13 | <0.01 | <0.01 |

**Values represent the means of two determinations in three separate experiments and are expressed as μg of lipid-bound sialic acid/10⁶ cells.**

**Table II**

| Treated with | Wild-type HL-60 | Retinoic acid-resistant HL-60 |
|--------------|----------------|----------------------------|
| Control | Retinoic acid | Control | Retinoic acid |
| μg hexose/10⁶ cells | | | |
| GalCer | 1.8 | 2.2 | 2.2 | 1.0 |
| LacCer | 13.7 | 20.1 | 9.9 | 4.3 |
| LcOseCer | 1.8 | 3.5 | 0.9 | 0.6 |
| nLcOseCer | 7.0 | 9.0 | 4.9 | 2.7 |
| Others* | 1.5 | 2.8 | 0.5 | 0.4 |

**Total**

25.8 37.6 18.4 9.0

*Cells were cultivated with or without retinoic acid (1 μM) for 4 days.

*Other neutral glycosphingolipids with longer sugar chains.

When wild-type HL-60 cells were cultivated in the presence of retinoic acid (1 μM) for 4 days, the cells were differentiated into mature granulocytes with a concomitant increase in the content of NeuAc-nLc (Table I), 2). During retinoic acid-induced granulocytic differentiation of wild-type HL-60 cells, 2 → 3 sialylparagloboside and 2 → 3 sialylparagloboside were increased, whereas 2 → 6 sialylparagloboside was decreased. On the other hand, when retinoic acid-resistant HL-60 cells were cultivated in the presence of retinoic acid (1 μM) for 4 days, the cells were not differentiated and remained promyelocytes morphologically, and no increase in the content of NeuAc-nLc was observed (Table I).

The decreased content of gangliosides in retinoic acid-resistant HL-60 cells may come from the specific defect of terminal sialylation or a concomitant decrease of the synthesis of glycosphingolipids. If the specific defect of terminal sialylation is responsible, it is expected that neutral glycosphingolipids, the precursors of gangliosides, would be accumulated in retinoic acid-resistant HL-60 cells. As shown in Fig. 1 and Table II, neutral glycosphingolipids were not accumulated in retinoic acid-resistant HL-60 cells. The total content of neutral glycosphingolipids of retinoic acid-resistant HL-60 cells...
The major component of neutral glycosphingolipids was LacCer in both types of cells. When the cells were cultivated in the presence of retinoic acid (1 μM) for 4 days, the total content of neutral glycosphingolipids in wild-type HL-60 cells was consistently increased and that in retinoic acid-resistant HL-60 cells was rather slightly decreased (Table II).

Granulocytic Differentiation of Retinoic Acid-resistant HL-60 Cells by NeuAc-nLc—When wild-type HL-60 cells are cultivated in the presence of retinoic acid or NeuAc-nLc, the cells are differentiated into mature granulocytes (5). If NeuAc-nLc mediates the differentiation induction by retinoic acid and the defective synthesis of NeuAc-nLc in response to retinoic acid is responsible for the lack of differentiation in retinoic acid-resistant HL-60 cells, it is expected that retinoic acid-resistant HL-60 cells could be differentiated into mature granulocytes when NeuAc-nLc are supplemented exogenously. When retinoic acid-resistant HL-60 cells were cultivated with 1 μM NeuAc-nLc prepared from mature granulocytes in the serum-free medium, an apparent morphological change reflecting differentiation along the granulocytic lineage was observed on day 2. On day 4, approximately 90% of the cells showed mature granulocytic cells morphologically (Fig. 2). The electron microscopic picture confirmed that HL-60 cells differentiated by NeuAc-nLc were mature granulocytes (Fig. 2). The granulocytic differentiation induced by NeuAc-nLc was also confirmed by the cytochemical lineage-specific esterase staining. When retinoic acid-resistant HL-60 cells were differentiated by NeuAc-nLc, the number of cells strongly positive for the granulocytic lineage-specific naphthol AS-D chloroacetate esterase activity was increased, whereas the number of cells positive for the monocytic lineage-specific α-naphthyl butyrate esterase activity was not altered (Table III). The number of cells capable of ingesting latex particles and reducing nitro blue tetrazolium was markedly increased by cultivating the cells in the presence of NeuAc-nLc (Table III). Retinoic acid-resistant HL-60 cells differentiated by NeuAc-nLc showed an increased O2-releasing capacity in response to PMA or a chemotactic peptide fMLP as compared with control cells. The representative time courses of O2 release stimulated by PMA or fMLP are shown in Fig. 3. The time courses of O2 release in mature HL-60 cells stimulated by PMA or fMLP were similar to those in normal granulocytes (14). The effect of NeuAc-nLc on the O2-releasing capacity was dependent on the concentration of NeuAc-nLc used as the inducer of differentiation (Figs. 3 and 4). As shown in Table IV, retinoic acid-resistant HL-60 cells differentiated by NeuAc-nLc expressed the surface membrane antigens recognized by monoclonal antibodies anti-OKM1 and anti-OKB2, whereas these cells did not express the antigens recognized by anti-OKM5 or anti-Mo2. Anti-OKM1 reacts on granulocytes and monocytes (15); anti-OKB2 reacts on granulocytes but not on monocytes (16); and anti-OKM5 and anti-Mo2 react on monocytes but not on granulocytes (17, 18). Thus, the findings with surface membrane antigens indicated that retinoic acid-resistant HL-60 cells differentiated by NeuAc-nLc were granulocytic cells. The differentiation of retinoic acid-resistant HL-60 cells by NeuAc-nLc was accompanied by inhibition of cell growth (Fig. 5). Inhibition of cell growth by NeuAc-nLc was observed without a significant loss of cell viability. The higher concentrations of NeuAc-nLc (>2 μM) were toxic to the cells.
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Differentiated by NeuAc-nLc, we analyzed the ganglioside composition in wild-type and retinoic acid-resistant HL-60 cells differentiated by NeuAc-nLc. As shown in Table I, the total content of gangliosides in wild-type HL-60 cells differentiated by NeuAc-nLc was not altered. However, the ganglioside composition was changed during NeuAc-nLc-induced granulocytic differentiation of wild-type HL-60 cells; 2 → 3 sialylparagloboside and 2 → 3 sialylnorhexaosylceramide were increased, whereas 2 → 6 sialylparagloboside was decreased. The changes in ganglioside composition of wild-type HL-60 cells differentiated by NeuAc-nLc were similar to those of wild-type HL-60 cells differentiated by retinoic acid (Table I). As with wild-type HL-60 cells, the total content of gangliosides was not significantly altered during NeuAc-nLc-induced granulocytic differentiation of retinoic acid-resistant HL-60 cells (<1.0 μg of lipid-bound sialic acid/10⁶ cells). Although minimal changes in ganglioside composition might occur in these cells, it was difficult to perform accurate analysis of ganglioside composition because of the limited amount of NeuAc-nLc available for differentiation induction and the low content of NeuAc-nLc in retinoic acid-resistant HL-60 cells.

**DISCUSSION**

By using wild-type HL-60 cells, we have recently demonstrated that retinoic acid induces granulocytic differentiation with a concomitant increase in the content of NeuAc-nLc and that NeuAc-nLc added exogenously to the medium induce granulocytic differentiation (1, 2, 5). These findings support the hypothesis that retinoic acid stimulates the synthesis of endogenous NeuAc-nLc, which, in turn, trigger or promote the differentiation of HL-60 cells into the granulocytic lineage. In this context, NeuAc-nLc added exogenously to the culture medium may be incorporated into the plasma membrane (19, 20); the lipophilic ceramide moiety being inserted into the lipid layer, and work as endogenous NeuAc-nLc do. In fact, we have observed that [³H]GM₃ is rapidly incorporated into the cells.³ The results of the present experiments with retinoic acid-resistant HL-60 cells provide additional evidence to support this hypothesis. The results presented here show that (a) the content of NeuAc-nLc of retinoic acid-resistant HL-60 cells was markedly diminished as compared with that of wild-type HL-60 cells; (b) retinoic acid induced neither granulocytic differentiation nor any increase of the content of NeuAc-nLc in retinoic acid-resistant HL-60 cells; and (c) NeuAc-nLc added exogenously to the medium induced differentiation of retinoic acid-resistant HL-60 cells into granulocytic lineage. These findings taken together suggest (a) that the synthesis of endogenous NeuAc-nLc is an important step for retinoic acid-induced granulocytic differentiation and this step could be bypassed or replaced by exogenous NeuAc-nLc, and (b) that the defective synthesis of endogenous NeuAc-nLc is responsible for the failure of differentiation induction in retinoic acid-resistant HL-60 cells by retinoic acid.

The analysis of the ganglioside composition of wild-type HL-60 cells differentiated by NeuAc-nLc revealed that although the total content of gangliosides was not altered, the ganglioside composition was changed during granulocytic differentiation. The changes in ganglioside composition of wild-type HL-60 cells differentiated by NeuAc-nLc were similar to those of wild-type HL-60 cells differentiated by retinoic acid, supporting the concept that granulocytic differentiation of HL-60 cells is closely associated with the changes in particular ganglioside molecules. The changes in the ganglioside composition of wild-type HL-60 cells differentiated by NeuAc-

³M. Nakamura and M. Saito, unpublished results.

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**Table IV**

Induction of mature granulocyte antigens in retinoic acid-resistant HL-60 cells by NeuAc-nLc

|       | OKM1 | OKB2 | OKM5 | Mo2 |
|-------|------|------|------|-----|
| Control | 23.3 | 1.6  | 0.1  | 0.2 |
| NeuAc-nLc-treated | 79.1 | 16.9 | 0.3  | 0.4 |

**Fig. 4.** Superoxide release in retinoic acid-resistant HL-60 cells cultivated with various concentrations of NeuAc-nLc for 4 days. The calculated values of the data shown in Fig. 3 were plotted. PMA (100 ng/ml) or FMLP (1 μM) was used as a stimulus.

**Fig. 5.** Inhibition of cell growth by NeuAc-nLc. Retinoic acid-resistant HL-60 cells were cultivated with various concentrations of NeuAc-nLc, and viable cells were counted on the indicated culture days. Each point represents the mean of three determinations. Vertical bars show standard deviations. No marked loss of viability was observed throughout the culture periods. ○, control; ●, 0.2 μM; ▲, 0.5 μM; △, 1 μM; □, 1.5 μM.

Changes in the Ganglioside Composition of HL-60 Cells Differentiated by NeuAc-nLc—To determine whether the content of NeuAc-nLc was actually increased in HL-60 cells differentiated by NeuAc-nLc, we analyzed the ganglioside...
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ncL do not necessarily implicate simple accumulation of exogenous gangliosides since we have recently observed that a large part of exogenous [14C]GlcNAc incorporated into wild-type HL-60 cells was rapidly degraded in the cells. It is possible that the changes in ganglioside composition in these cells may reflect the increased glycosphingolipid metabolism during differentiation. These findings and the negligible alteration in the total content of gangliosides during NeuAc-nLc-induced granulocytic differentiation of retinoic acid-resistant HL-60 cells taken together suggest that persistent accumulation of a large amount of NeuAc-nLc is not necessarily required for promotion of cell differentiation. It is likely that either accumulation of a small amount of a particular NeuAc-nLc molecule or a transient association of particular NeuAc-nLc molecules with the plasma membrane may be sufficient for promotion of cell differentiation.

In retinoic acid-resistant HL-60 cells, the content of NeuAc-nLc was markedly diminished without any accumulation of neutral glycosphingolipids, the precursors of gangliosides, suggesting that the decreased content of gangliosides could not be explained by the defect of terminal sialylation alone. It is likely that in addition to the defect of terminal sialylation, a general decrease of the synthesis of glycosphingolipids may be responsible for the decreased content of gangliosides in retinoic acid-resistant HL-60 cells.

Retinoic acid is believed to exert its biological effect in various types of cells by interacting with a specific cytoplasmic retinoic acid-binding protein (21-24). However, it appears that modulation of tumor cell growth rate by retinoic acid is not necessarily mediated by cytoplasmic retinoic acid-binding protein since the sensitivity of the cells to growth inhibition by retinoic acid does not correlate with the level of cytoplasmic retinoic acid-binding protein in the cell (25). In addition, leukemic cells, including HL-60 and KG-1 cells, are reported to lack such a binding protein (26). Furthermore, it has been reported that retinoic acid-induced differentiation is initiated at the cell surface since granulocytic differentiation occurs when HL-60 cells are cultured with retinoic acid immobilized on a solid substrate (27). It is unknown how retinoic acid interacts with the cell surface membrane and what kinds of intracellular signals are produced by retinoic acid. The present and our previous experiments (5) suggest that the synthesis of endogenous NeuAc-nLc is an important step for granulocytic differentiation induced by retinoic acid. Thus it is possible that the defective enzyme system required for the synthesis of NeuAc-nLc may be responsible not only for the decreased content of NeuAc-nLc but also for the failure of differentiation induction in retinoic acid-resistant HL-60 cells by retinoic acid. Another possibility is that the interaction between retinoic acid and the cell surface membrane may fail to activate the enzymes required for the synthesis of NeuAc-nLc in retinoic acid-resistant HL-60 cells.

It has been reported that exogenously added gangliosides alter the growth of various types of cells (28-34). Exogenous gangliosides inhibit the action of several growth factors as well as the tyrosine kinase activity associated with the growth factor receptors (31, 32); inhibit the proliferation of lymphocytes stimulated by lectins, antigens, or interleukin 2 (33); sensitize tumor cells to growth inhibitors (29); and stimulate the proliferation of astroglial (34) and neuroblastoma cells (30). Furthermore, the B subunit of cholera toxin, which binds specifically to ganglioside Gm1 on the cell surface membrane, has been shown to stimulate the proliferation of thymocytes (35) and quiescent nontransformed mouse 3T3 cells and to inhibit the growth of ras-transformed 3T3 cells and rapidly dividing normal 3T3 cells (36). These observations and the present experiments strongly suggest that gangliosides play an important role in the regulation of cell differentiation as well as cell growth. The molecular basis for ganglioside-induced stimulatory or inhibitory effects remains to be determined. One possible mechanism is that the increased content of particular ganglioside molecules on the cell surface membrane may affect the cell metabolism by altering the functions or the enzyme activities of certain glycoproteins on the cell surface. It has been reported recently that protein kinases regulated by gangliosides are present in guinea pig brain (37, 38). Another possibility is that the interaction between the particular ganglioside molecules and the cell surface membrane may produce second intracellular messengers that are not yet identified. Ganglioside-specific binding protein has been demonstrated recently on rat brain membranes (39).

There are several reports of patients with promyelocytic leukemia, who have apparently benefited from the systemic therapy with retinoic acid (40-42). The present experiments indicate that NeuAc-nLc could be beneficial to the treatment of certain types of myelogenous leukemia in which leukemic cells become resistant to differentiation induction by retinoic acid. Further investigations into the mechanisms of retinoic acid- and NeuAc-nLc-induced differentiation of HL-60 cells may help to shed light on the pathophysiology in differentiation and proliferation of leukemic cells.

Acknowledgments—We wish to thank Prof. F. Takaku (University of Tokyo), Prof. Y. Miura (Jichi Medical School), and Prof. Y. Nagai (University of Tokyo) for their valuable comments and M. Todoroki and Y. Enomoto for their technical assistance.

REFERENCES

1. Nojiri, H., Takaku,F., Tetsuoka, T., Motoroishi, K., Miura, Y., and Saito, M. (1984) Blood 64, 534-541
2. Nojiri, H., Takaku, F., Ohba, M., Miura, Y., and Saito, M. (1985) Cancer Res. 45, 6100-6106
3. Saito, M., Terui, Y., and Nojiri, H. (1985) Biochem. Biophys. Res. Commun. 132, 223-231
4. Nojiri, H., Takaku, F., Terui, Y., Miura, Y., and Saito, M. (1986) Proc. Natl. Acad. Sci. U. S. A. 83, 782-786
5. Nojiri, H., Kitagawa, S., Nakamura, M., Kirito, K., Enomoto, y., and Saito, M. (1988) J. Biol. Chem. 263, 7443-7446
6. Gallagher, R. E., Giangulo, D. A., Chang, C.-S., Glover, C. J., and Felsted, R. L. (1986) Blood 68, 1402-1406
7. Gallagher, R. E., Billo, P. A., Ferrari, A. C., Chang, C.-S., Yen, R.-W. C., Nickolos, W. A., and Muly, E. C. III (1985) Leukemia Res. 9, 967-986
8. Fukuda, M. N., Dell, A., Oates, J. E., Wu, P., Klock, J. C., and Fukuda, M. (1985) J. Biol. Chem. 260, 1067-1082
9. Hakomori, S., Patterson, C. M., Nadelman, E., and Sekiguchi, K. (1983) J. Biol. Chem. 258, 11819-11822
10. Hirabayashi, Y., Hamako, A., Matsuura, M., Matusbara, T., Tagawa, M., Wakahayashi, S., and Taniguchi, M. (1985) J. Biol. Chem. 260, 13328-13333
11. Suzuki, K. (1964) Life Sci. 3, 1227-1233
12. Francois, C., Marchall, R. D., and Neuberger, A. (1962) Biochem. J. 83, 335-341
13. Dubois, M., Gilles, K. A., Hamilton, J. K., Rebers, P. A., and Smith, F. (1956) Anal. Chem. 28, 350-356
14. Tagawa, S., Ohba, M., Nojiri, H., Kakimura, K., Saito, M., Takaku, F., and Miura, Y. (1984) J. Clin. Invest. 73, 1062-1071
15. Wright, S. D., Rao, P. E., Van Voorhis, W. C., Craigmyte, L. S., Iida, K., Talle, M. A., Westberg, E. F., Goldstein, G., and Smith, S. C. (1983) Proc. Natl. Acad. Sci. U. S. A. 80, 5699-5703
16. Mittler, R. S., Talle, M. A., Carpenter, K., Rao, P. E., and Goldstein, G. (1983) J. Immunol. 131, 1754-1761
17. Talle, M. A., Rao, P. E., Westberg, E., Allegar, N., Makowski, M., Mittler, R. S., and Goldstein, G. (1980) Cell. Immunol. 78, 83-99
18. Todd, R. F., III, and Schlossman, S. F. (1982) Blood 59, 775-786
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19. Laine, R. A., and Hakomori, S. (1973) Biochem. Biophys. Res. Commun. 54, 1039–1045
20. Kanda, S., Inoue, K., Nojima, S., Utsumi, H., and Wiegandt, H. (1982) J. Biochem. (Tokyo) 91, 1707–1718
21. Jetten, A. M., Jetten, M. E. R., Shapiro, S. S., and Poon, J. P. (1979) Exp. Cell Res. 119, 289–299
22. Jetten, A. M., and Jetten, M. E. R. (1979) Nature 281, 180–182
23. Lotan, R., Neumann, G., and Lotan, D. (1980) Cancer Res. 40, 1097–1102
24. Schindler, J., Matthaei, K. I., and Sherman, M. I. (1981) Proc. Natl. Acad. Sci. U. S. A. 78, 1077–1080
25. Lotan, R., Ong, D. E., and Chytil, F. (1980) J. Natl. Cancer Inst. 64, 1259–1262
26. Douer, D., and Koeffler, H. P. (1982) J. Clin. Invest. 69, 277–283
27. Yen, A., Reece, S. L., and Albright, K. L. (1984) Exp. Cell Res. 152, 493–499
28. Keenan, T. W., Schmid, E., Franke, W. W., and Wiegandt, H. (1975) Exp. Cell Res. 92, 259–270
29. Kinders, R. J., Rintoul, D. A., and Johnson, T. C. (1982) Biochem. Biophys. Res. Commun. 107, 663–669
30. Tsuji, S., Arita, M., and Nagai, Y. (1983) J. Biochem. (Tokyo) 94, 303–306
31. Bremer, E. G., Hakomori, S., Bowen-Pope, D. F., Raines, E., and Ross, R. (1984) J. Biol. Chem. 259, 6818–6825
32. Bremer, E. G., Schlessinger, J., and Hakomori, S. (1986) J. Biol. Chem. 261, 2434–2440
33. Robb, R. (1986) J. Immunol. 136, 971–976
34. Kato-Hemba, R., Facci, L., Shaper, S. D., and Varon, S. (1986) J. Cell. Physiol. 126, 147–153
35. Spiegel, S., Fishman, P. H., and Weber, R. J. (1985) Science 230, 1285–1287
36. Spiegel, S., and Fishman, P. H. (1987) Proc. Natl. Acad. Sci. U. S. A. 84, 141–145
37. Chan, K-F. J. (1987) J. Biol. Chem. 262, 5248–5255
38. Chan, K-F. J. (1988) J. Biol. Chem. 263, 568–574
39. Tiemeyer, M., Yasuda, Y., and Schnaar, R. L. (1989) J. Biol. Chem. 264, 1671–1681
40. Flynn, P., Miller, W., Weisdorf, D., Arthur, D., Brunning, R., and Branda, R. (1983) Blood 62, 1211–1217
41. Nilsson, B. (1984) Br. J. Haematol. 57, 365–371
42. Daenen, S., Vellenga, E., van Dobbenburgh, O., and Halie, M. (1986) Blood 67, 559–561
43. Nomenclature Committee of the International Union of Pure and Applied Chemistry (1977) Lipids 12, 455–468