Human Myelomonocytic Cell Line THP-1 Produces a Novel Growth-promoting Factor with a Wide Target Cell Spectrum

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ABSTRACT

Conditioned medium from a human myelomonocytic cell line THP-1 promoted the growth of a wide variety of cell types, i.e., human and mouse myeloid cells (HL-60, U937, K562, and M1), mouse T-cells (EL-4), human B cells (Daudi and Raji), mouse mastocytoma cells (IC-2), human melanoma cells (A375-C6), mouse transformed fibroblast cells (L929), human lung fibroblast cells (TIG-1), and mouse bone marrow fibroblast/stromal-like cells. The growth-promoting activity was acid-labile. The activity was lost at 50°C for 5 min but completely lost in 5 min at 70°C. The activity was resistant to 50°C for 5 min but completely lost in 5 min at 70°C. The activity was resistant to treatment with trypsin but sensitive to chymotrypsin α, Pronase E, and proteinase K, indicating the proteinous nature of this activity. The activity was lost by dithiothreitol and 2-mercaptoethanol. Molecular weight (M₀, 50,000-70,000) was estimated by gel filtration-high performance liquid chromatography. After the sequential anion exchange, hydrophobic, and hydroxylapatite high performance liquid chromatography, the partially purified factor exhibited the same target cell spectrum as the conditioned medium.

INTRODUCTION

Macrophages and monocytes play important roles in many host reactions. Infiltration by these cells is observed in tumors, normal wound repair, and pathological tissue. They are thought to regulate the growth and differentiation of normal and tumor cells in either a positive or negative manner, through the production of a variety of cytokines including IL-1, IL-6, IL-8, TNF, IFN, and CSF (1). We have investigated a differentiation-inducing factor for a mouse myeloid leukemic cell line (M1) in conditioned medium from a human myelomonocytic cell line, THP-1. M1 cell differentiation into macrophages usually accompanies the inhibition of cell proliferation (2). Proliferation of M1 cells was unexpectedly stimulated by the conditioned medium. Since M1 and THP-1 cells are myeloid leukemia cells, the first expectation was that the growth-promoting activity might be attributed to an autocrine growth factor specific to myeloid leukemia cells. However, the conditioned medium also stimulated the proliferation of a wide variety of cell types, including human and mouse cell lines, myeloid, T-, B, mastocytoma, melanoma, and fibroblast cells. This article reports the characterization and partial purification of this novel growth-promoting factor.

MATERIALS AND METHODS

Reagent. RPMI 1640 was purchased from Sigma Chemical Co. (St. Louis, MO); FBS was from Hyclone Laboratories (Logan, UT); trypsin was purchased from Difco Laboratories (Detroit, MI); chymotrypsin α was from ICN (Cleveland, OH); Pronase E was from Kaken Chemical Co. (Tokyo, Japan); proteinase K was from Merck (Darmstadt); dithiothreitol was from Nacalai Tesque, Inc. (Kyoto, Japan); 2-ME was from Wako Pure Chemical Industries, Ltd. (Osaka, Japan); and human recombinant M-CSF was from Genzyme Co. (Cambridge, MA). Human recombinant G-CSF and GM-CSF were, respectively, generous gifts from Chugai Pharmaceutical Co. (Tokyo, Japan) and Genetics Institute (Cambridge, MA).

Cell Culture. Human myelomonocytic cell line THP-1, obtained from the American Type Culture Collection, was freed of contaminant Mycoplasma fermentans by Dr. A. Nordin (Francis Scott Key Medical Center, National Institute on Aging, NIH, Baltimore, MD). Human promyelocytic cell line HL-60 was provided by Dr. H. Hemmi of Tohoku University (Sendai, Japan). Human histiocytic cell line U937, human EB virus transformed B cell line Raji, and human lung fibroblast cell line TIG-1 were from the Japanese Cancer Research Resources Bank-Cell (Tokyo, Japan). Mouse mastocytoma cell line IC-2 was from Dr. K. Inoue of Tokyo University (Tokyo, Japan). Human EB virus transformed B cell line Daudi, human chronic myelogenous leukemia cell line K562, and mouse T-cell line EL-4 were provided by Dr. T. Fujita of Fukushima Medical College (Fukushima, Japan). Human melanoma cell line A375-C6 and mouse transformed fibroblast cell line L929 were maintained in this laboratory. THP-1, HL-60, U937, K562, M1, EL-4, Daudi, Raji, A375-C6, TIG-1, and L929 cells were maintained in RPMI 1640 containing 100 units/ml of Penicillin G, 100 µg/ml of streptomycin, 15 µg HEPES, and 5% heat-inactivated FBS. An IL-3-dependent cell line IC-2 was maintained in RPMI 1640, antibiotics, HEPES, 5 x 10⁻⁵ M 2-ME, and 10% conditioned medium from WEHI-3 cells as a source of IL-3.

Assay of Cell Proliferation. Cells suspended in RPMI 1640 supplemented with antibiotics, HEPES, 5% FBS, and test samples were cultured in the wells of flat-bottomed microtiter plates (100 µl of 1 x 10⁴ cells each; Falcon, Lincoln, NJ) at 37°C in air supplemented with 5% CO₂ for 3 days. Adherent cells, A375-C6, TIG-1, and L929, were detached from culture plates with 0.05% trypsin-0.02% EDTA to make cell suspensions. IC-2 cells were cultured in maintenance medium with test samples but without conditioned medium from WEHI-3 cells. Except for A375-C6, TIG-1, L929 cells, thymocytes, spleen cells and bone marrow cells, cell proliferation was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (3). Proliferation of A375-C6, TIG-1, and L929 cells was determined by a dye-staining method with crystal violet (4). Proliferation was expressed as A₅₉₀, percentage of control or units. Percentage control was calculated as:

\[
\% \text{ of control} = \frac{A_{590} \text{ in cells cultured in medium with samples}}{A_{590} \text{ in cells cultured in medium alone}} \times 100
\]

One unit of proliferation activity was defined as the reciprocal of the dilution of test samples exhibiting 50% of maximum stimulation.

Thymocytes and spleen cells were obtained from ICR mice (female, 6-10 weeks old; Japan SLIC, Inc., Shizuoka, Japan). Thymocytes and spleen cells were cultured in the wells of flat-bottomed microtiter plates (200 µl of 2 x 10⁴ cells each) in RPMI 1640 supplemented with antibiotics, HEPES, 5% FBS, and 2.5 x 10⁻⁵ M 2-ME in the presence of samples for 72 h. For thymocyte culture concanavalin A (0.5 µg/ml) was added. Cultures were pulsed with 0.5 µCi/well of [³H]thymidine (2 Ci/mmol; New England Nuclear, Boston, MA) during the final 4 h of incubation and harvested, and the radioactivity incorporated into DNA was determined in a liquid scintillation counter (Aloka, Tokyo, Japan).

Stimulation of DNA Synthesis in Liquid Cultures of CSF Activity. Thymidine incorporation assay of CSF activity was performed according to the method of Gaffney et al. (5). Unfractioned mouse bone marrow cells from ICR mice were inoculated into a flat-bottomed microtiter plate at 1 x 10⁵ cells/well in 200 µl RPMI 1640 containing antibiotics, HEPES, and 5% FBS. Cells were incubated in the presence or absence of THP-1-conditioned medium or human

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1 To whom requests for reprints should be addressed.

2 The abbreviations used are: IL, interleukin; HPLC, high performance liquid chromatography; TNF, tumor necrosis factor; IFN, interferon(s); CSF, colony-stimulating factor(s); FBS, fetal bovine serum; 2-ME, 2-mercaptoethanol; HEPES, 4-(2-hydroxyethyl)-1-piperazineneethanesulfonic acid; PBS, phosphate-buffered saline; LIF, leukemia-inhibitory factor; G-CSF, granulocyte CSF; GM-CSF, granulocyte-macrophage CSF; M-CSF, macrophage CSF; EB virus, Epstein-Barr virus.

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G-CSF for 5 days before labeling with [3H]thymidine (2 μCi/well; 5 Ci/mmol) for 18 h. Radioactivity was counted in a liquid scintillation counter.

**Colony Formation in Agarose.** Agarose medium (0.5 ml), consisting of 0.5% agarose (Nacalai, Tokyo, Japan), 10% FBS, and RPMI 1640, was added to each well in a 24-well flat-bottomed plate (Falcon). The bottom layer of agarose was overlaid with 0.5 ml of 0.3% agarose medium containing 400 A375 or 100 L929 cells with or without THP-1-conditioned medium. After the cells were cultured at 37°C for 1 week, colonies consisting of more than 10 cells were counted.

**Conditioned Medium of THP-1 Cells.** THP-1 cells were grown in culture flasks (Falcon) or in spinner culture bottles (HARIO, Tokyo, Japan), collected by centrifugations, and washed twice with RPMI 1640. Cells (1 x 10⁶ cells/ml) were cultured in serum-free RPMI 1640 supplemented with antibiotics and HEPES.

**Treatment of Conditioned Medium.** For measurement of the heat stability of the growth-promoting activity, the conditioned medium was diluted 5-fold with PBS (pH 7.4) and heated to either 50°C or 70°C for 5 min. After cooling, samples were further diluted 5-fold with medium containing 5% FBS. Acid stability was assessed following 5-fold dilution of the conditioned medium with either 1.0 M acetic acid or 1.0 M formic acid and incubation at 4°C for 16 h. After the addition of bovine serum albumin (final concentration, 33 μg/ml), samples were dialyzed against PBS and diluted 5-fold with medium containing 5% FBS. Susceptibility of the activity to proteases was examined by incubation of the conditioned medium (diluted with PBS to 50 μg protein/ml) with equal volumes of proteases (50 μg/ml), trypsin, chymotrypsin E, or proteinase K at 37°C for 16 h. After incubation, 1 mM phenylmethylsulfonyl fluoride was added to the samples which were then diluted 5-fold with medium containing 5% FBS. For the examination of the effect of reducing reagents, the conditioned medium (diluted with PBS to 100 μg protein/ml) was incubated with 100 mM dithiothreitol or 5% 2-ME at room temperature for 1 h. Then bovine serum albumin was added (final concentration, 33 μg/ml) and the mixture was dialyzed against PBS overnight at 4°C and diluted 5-fold with medium containing 5% FBS. All samples were sterilized by filtration (pore size, 0.45 μm; Toyoo Roshi Kaisha, Ltd., Tokyo, Japan).

**HPLC.** Characterization and purification were carried out at room temperature using a Shimadzu Model LC-4A HPLC system (Shimadzu, Tokyo, Japan).

**Gel Filtration HPLC.** The conditioned medium was concentrated on an Amicon diaflow membrane, YM5 (M, cutoff, 5000), and dialyzed against PBS. Samples were applied to a 7.5-mm x 60-cm TSK-gel G3000SW column (TOSOH, Tokyo, Japan) equilibrated with PBS. Fractions (1 ml) were collected at a flow rate of 0.5 ml/min. The column was calibrated with ferritin (M, 450,000), bovine serum albumin (M, 67,000), ovalbumin (M, 43,000), and myoglobin (M, 17,800).

**DEAE HPLC.** Concentrated conditioned medium was dialyzed against 0.02 M sodium phosphate buffer (pH 7.4) and applied to a 7.5-mm x 75-mm TSK-gel DEAE-5PW column (TOSOH, Tokyo, Japan) equilibrated with the same buffer. The starting buffer was 0.02 M sodium phosphate buffer (pH 7.4) and the limiting buffer was 0.02 M sodium phosphate buffer and 1.0 M NaCl (pH 7.4). Fractions (1 ml) were collected at a flow rate of 1.0 ml/min.

**Hydrophobic HPLC.** Samples from DEAE HPLC were dialyzed against 1.8 M (NH₄)₂SO₄-0.1 M sodium phosphate buffer (pH 6.8) and applied to a 7.5-mm x 75-mm TSK-gel Phenyl-5PW column (TOSOH, Tokyo) equilibrated with the same buffer. The starting buffer was 1.8 M (NH₄)₂SO₄-0.1 M sodium phosphate buffer (pH 6.8) and the limiting buffer was 0.1 M sodium phosphate buffer (pH 6.8). Fractions (1 ml) were collected at a flow rate of 1.0 ml/min.

**Hydroxyapatite HPLC.** Samples from hydrophobic HPLC were dialyzed against 0.01 M sodium phosphate buffer (pH 6.8)-0.3 M CaCl₂ and applied to a 7.8 x 100-mm Bio-Gel HPTH column (Bio-Rad, Richmond, CA) equilibrated with the same buffer. The starting buffer was 0.01 M sodium phosphate buffer (pH 6.8)-0.3 M CaCl₂ and the limiting buffer was 0.5 M sodium phosphate buffer (pH 6.8) and 0.1 M CaCl₂. Fractions (1 ml) were collected at a flow rate of 1.0 ml/min.

**Electrophoresis.** Analytical sodium dodecyl sulfate-polyacrylamide gel electrophoresis was performed according to the method of Laemmli (6) in 12.5% polyacrylamide gel using a vertical slab mini-gel apparatus. Molecular weight standards (Pharmacia) were: phosphorylase b, M, 94,000; bovine serum albumin, M, 67,000; ovalbumin, M, 43,000; carbonic anhydrase, M, 30,000; soybean trypsin inhibitor, M, 20,100; alpha-lactalbumin, M, 14,400. Protein bands were visualized by silver stain using commercial kits (Wako).

**RESULTS**

**Growth-promoting Activity of Conditioned Medium from THP-1 Cells for Various Target Cells.** Conditioned medium was obtained from THP-1 cells in order to determine its growth-promoting activity with various target cells. Thus, cells were cultured for 3 days with varying doses of the conditioned medium in the presence of 5% FBS. Fig. 1 shows that the growth of HL-60, U937, Daudi, and EL-4 cells was promoted by the conditioned medium in a dose-dependent manner. The conditioned medium also promoted, in a dose-dependent manner, the growth of M1, K562, Raji, IC-2, A375-C6, TIG-1, and L929 cells (data not shown). However, the growth of THP-1 cells was not affected. The conditioned medium also promoted the thymidine incorporation of 5 days cultured mouse bone marrow cells (Fig. 2). The stimulation was greater than that of recombinant G-CSF. Morphological examination indicated, however, that the conditioned medium promoted the growth of fibroblast/stromal-like cells and no macrophages/granulocytes were observed. In contrast, abundant granulocytes were observed in G-CSF-stimulated bone marrow cell cultures. In contrast to the conditioned medium from THP-1 cells, human G-CSF, M-CSF, and GM-CSF were unable to promote the growth of HL-60 target cells (data not shown). The conditioned medium, however, failed to stimulate the proliferation of thymocytes and spleen cells and the colony formation (either number or size) of A375-C6 or L929 cells cultured in agarose (data not shown).

**Dependence of the Growth-promoting Activity on the Initial Cell Density.** Serum concentrations and initial cell densities were varied to determine their effects on the growth-promoting activity. HL-60 cells were cultured in the presence of 1, 2, 3, 4, 5, or 10% FBS, which exhibited no effect on the growth promoting activity (data not shown). In contrast, the activity appeared to depend on the initial cell density (Fig. 3). Since the activity was evident with a small cell, density assays, including the experiment shown in Fig. 1, were conducted at the initial density of 1 x 10⁴ cells/ml. In contrast, THP-1 cell growth was not promoted even when the cell number decreased to 1 x 10¹⁰ cells/ml.

**Kinetics of the Growth-promoting Activity Production.** The kinetics of the growth-promoting activity production were studied by
culturing THP-1 cells in serum-free medium. Fig. 4 shows the results of experiments in which conditioned medium was collected continuously for the indicated periods. The activity in the conditioned medium increased in a time-dependent manner. The number of dead cells, determined by the trypan blue dye-exclusion test, rapidly increased after 5 days in culture (data not shown). Therefore, conditioned medium was collected after 4 days for characterization and purification.

**Characterization of the Growth-promoting Activity.** Effects of various treatments on the growth-promoting activity of the conditioned medium are shown in Table I. The activity was resistant to 50°C for 5 min but was lost completely when heated at 70°C for the same period. Treatment with 1.0 M acetic or formic acids completely inactivated the activity. Treatment with trypsin did not affect the activity, but the activity was sensitive to chymotrypsin α, Pronase E, and proteinase K. Control experiments demonstrated that these proteases, when added to the conditioned medium after the addition of phenylmethylsulfonyl fluoride and dilution with serum-containing medium, did not inhibit the growth-promoting activity of the conditioned medium (data not shown). Exposure to reducing reagents resulted in total inactivation of the activity.

**Gel Filtration Chromatography.** The molecular size of the growth-promoting activity was estimated by running the conditioned medium through a gel filtration column. Fig. 5 shows that the activity eluted at a position equivalent to a Mₐ range of 50,000–70,000.

**Partial Purification of the Growth-promoting Activity.** Results of gel filtration column chromatography and other treatments demonstrated the proteinous nature of the growth-promoting activity. Therefore, attempts were made to purify the growth-promoting factor. Pooled conditioned medium was concentrated and applied to a TSK-

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**Table I Biochemical characterizations of growth-promoting activity in the conditioned medium from THP-1 cells**

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Growth-promoting activity (units/ml)</th>
<th>% of inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>50°C for 5 min</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>70°C for 5 min</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Acid treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>1 M acetic acid</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1 M formic acid</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Enzyme treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Trypsin</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>Chymotrypsin α</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Pronase E</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Proteinase K</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Reducing reagents treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>5% 2-ME</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>100 mM dithiothreitol</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

*a* Conditioned medium from THP-1 cells was subjected to different treatments as described in “Materials and Methods.” The growth-promoting activity was determined for HL-60 cells.
HUMAN MONOCYTIC CELL-DERIVED GROWTH FACTOR

Fig. 5. Gel filtration HPLC of the conditioned medium. Concentrated conditioned medium from THP-1 cells was applied to a TSK-gel G3000SW column as described in "Materials and Methods." The growth-promoting activity was determined for HL-60 cells in each fraction. Arrows, times at which reference proteins were eluted from the column (FER, ferritin; BSA, bovine serum albumin; EGA, egg albumin; MYO, myoglobin).

gel DEAE-5PW column. Major activity appeared at 0.12–0.20 M NaCl (Fig. 6). The active fractions (fractions, 9–12) were pooled and further applied to a TSK-gel Phenyl-5PW column (Fig. 7). This activity appeared as a single peak at 0.13–0.27 M (NH₄)₂SO₄. The active fractions (fractions 29 and 30) were pooled and applied to a Bio-Gel HPHT column. Fig. 8 shows that the activity eluted in 0.085–0.12 M sodium phosphate buffer. This specific activity could be increased 346-fold by three HPLC steps (Table 2). These fractions (fractions 12 and 13) were pooled and analyzed with sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Under both reducing and nonreducing conditions, the active fraction contained two major (M, 52,000 and M, 29,000) and two minor bands (M, 39,000 and M, 21,000) (Fig. 9). The partially purified growth factor exhibited the same wide target cell spectrum as the conditioned medium (data not shown).

DISCUSSION

In this study, THP-1 cells appeared to produce a novel growth-promoting activity with a wide range of target cells, including not only tumor cells but also normal fibroblast cells. This activity was acid labile and heat inactivated in 5 min at 70°C. Because of sensitivity to chymotrypsin α, Pronase E and proteinase K, the active molecule(s) is considered to be a protein. This activity was also sensitive to reducing reagents suggesting that intra- or intermolecular sulfide bonds or sulfhydryl residues are essential for its activity. Gel filtration column chromatography indicated that the molecular weight of this factor was 50,000–70,000.

Among the cell lines examined, only THP-1 cells were refractory to this growth-promoting activity. This suggests that THP-1 cells may
produce their own growth factor. Antibodies against this growth factor would help to discern whether it acts in an autocrine manner.

The growth-promoting activity was dependent on an initial low cell density, not promoting the proliferation of cells cultured with an initial high cell density. Therefore, this activity appears to stimulate the cell proliferation when culture conditions were not optimal. The reason that the cell proliferation was promoted only at low cell density is not known. We could not observe the stimulating effects on colony formation of A375-C6 or L929 cells cultured in soft agarose, although the proliferation of these cells in culture plates was augmented. This might be due to the different culture conditions. Because many transformed hematopoietic cell lines are reported to produce autocrine growth factor (7), we investigated whether the conditioned medium from HL-60 cells also possesses cell growth-promoting activity. However, the conditioned medium from HL-60 cells showed neither growth-promoting activity nor exhibited any synergistic effects compared to that of THP-1 conditioned medium, with respect to the proliferation of THP-1 and HL-60 cells (data not shown). The kinetics of the factor produced by THP-1 cells indicate that the activity in the conditioned medium increased continuously for up to 8 days. However, the dead cell number rapidly increased after 5 days. Therefore, the activity after 5 days may result from the leakage from degenerating cells.

Monocytic cell lines such as THP-1 cells are known to produce a wide variety of cytokines, including IL-1 (8), IL-6, IL-8 (9), TNF, IFN, CSF (5), and LIF (10). This growth-promoting activity is unlikely to be a constituent of serum, such as epidermal growth factor, fibroblast growth factor, and platelet-derived growth factor, since the
growth factor activity was observed in serum concentrations from 1 to 10%. This laboratory, as well as others, reported that M1 cell growth was inhibited by IL-1, IL-6, TNF (11, 12), and LIF (13). Therefore, this THP-1 factor is different from IL-1, IL-6, TNF, and LIF. This was ascertained by the observation that this factor stimulated the growth of A375-C6 cells the growth of which was inhibited by IL-1, IL-6, TNF, and IFN-α, -β (14, 15), and -γ. 3 THP-1 cells are reported to produce M-CSF (5). However, recombinant human M-CSF, G-CSF, or GM-CSF did not stimulate the proliferation of HL-60 target cells. Although the THP-1-derived factor stimulated the proliferation of mouse bone marrow cells, the proliferative cells were fibroblast/stromal-like cells, whereas human M-CSF can stimulate the growth of mouse bone marrow cells (16). This finding supports the notion that M-CSF and the THP-1-derived growth-promoting activity are different molecular entities. The proliferation of the IL-3-dependent cell line IC-2 was also stimulated. However, the THP-1 factor did not stimulate the proliferation of another IL-3-dependent mouse myeloma cell line, FDC-P2 (data not shown), excluding IL-3 as an effector molecule. Except for TNF and M-CSF, the complementary DNA of which have been cloned, hepatocyte growth factor (M, 100,000–150,000) and IL-12 (M, 70,000) are similar to the THP-1 factor in their molecular size. Hepatocyte growth factor is sensitive to trypsin (17), while the THP-1 factor is resistant. IL-12 is produced by the EB virus transformed B cell line, and this cytokine stimulates the proliferation of only limited cell types such as natural killer and activated T-cells (18).

The most interesting aspect of this factor is its wide variety of target cell types. Myeloid, T-, B, mastocytoma, melanoma, and transformed and normal fibroblast cell growth were stimulated. Cytokine or growth factor with such activity has not yet been reported. It was of note that this target cell spectrum was not lost after fractionation by sequential column chromatography. Whether this growth factor is a novel cytokine or is related to other known factor will have to await further studies.

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REFERENCES

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