Transforming Growth Factors in Solid Human Malignant Neoplasms

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ABSTRACT

Surgically removed solid human benign and malignant neoplasms and nonneoplastic tissues were examined for the presence of transforming growth factors (TGFs). TGFs are polypeptide growth factor-like substances which cause the appearance of a reversible neoplastic phenotype in nontransformed, anchorage-dependent cells in culture, including the induction of the ability to grow while suspended in semisolid medium. Acid-ethanol extracts from adenocarcinomas of the breast, colon, kidney, and ovary; fibrosarcoma and leiomyosarcoma; Hodgkin’s lymphoma; fibroadenoma of the breast; uterine leiomyoma; and nonneoplastic kidney and lung were found to cause growth in soft agar of both nontransformed mouse AKR-2B and rat NRK cells. This colony-stimulating activity, where tested, was heat and acid stable but was destroyed by trypsin and dithiothreitol treatment, indicating that the activity is due to a polypeptide with disulfide bonds. Extracts from several of the tumors provided sufficient material for purification by molecular sieve chromatography. Peaks of colony-stimulating activity from a Bio-Gel P-60 column eluted with 1 M acetic acid were detected in the M<sub>app</sub> range of 4,000 to 25,000. This activity required the presence of a polypeptide in the fraction and TGF<sub>nl</sub> fraction, denoting small (less than 6,000) and large (12,000 to 20,000) apparent molecular weights, respectively. The TGF<sub>a</sub> and TGF<sub>nl</sub> activities were present in malignant and nonneoplastic (kidney and lung) tissue, whereas the TGF<sub>ns</sub> activity predominated in benign neoplasms. These TGFs exhibited no competition with epidermal growth factor for binding to the epidermal growth factor receptor, and the TGF<sub>nl</sub> activity was potentiated by epidermal growth factor.

INTRODUCTION

TGFs are a family of heat- and acid-stable polypeptides which reversibly cause nontransformed, anchorage-dependent cells to assume a transformed morphology and to form progressively growing colonies in soft agar (4, 8, 11, 15). It has been suggested that autostimulation by endogenously produced growth factors may be one mechanism for a stage in neoplastic progression (18). The original description of TGF activity was that of DeLarco and Todaro (4) who described the properties of a polypeptide, SGF, which is released into culture medium by MSV-transformed mouse fibroblasts. They found that SGF competed with EGF for binding to the EGF receptor, but was different from EGF because it did not cross-react with EGF antibodies and did cause growth in soft agar of rat NRK cells (4, 5). A study of the growth factors produced by several human tumor cell lines conducted by Todaro et al. (19) showed evidence for production of 2 distinct TGFs which stimulated NRK cells to form colonies in soft agar. The major TGF, produced only by the cells which display low numbers of EGF receptors, was shown to have strong competition for binding to the EGF receptor. A much smaller peak of TGF activity was present in tumor lines with both high and low EGF receptor numbers and did not show significant competition for binding to the EGF receptor (19). Using a human tumor cell line selected for the ability to grow in culture and for low levels of EGF receptor, Marquardt and Todaro (7) have been able to purify and to delineate the amino acid composition of a TGF which shows strong competition for binding to the EGF receptor.

Other TGFs which do not compete for binding to the EGF receptor and which cause colony formation by nontransformed mouse AKR-2B cells in soft agar have been isolated from medium conditioned by chemically transformed mouse cells (8), 17-day mouse embryos (12), FBS, and bovine and human platelets (3). Roberts et al. (14) described similar TGF activity without associated EGF receptor binding in nonneoplastic mouse tissue and reported that this NRK colony-stimulating activity was potentiated by adding optimal amounts of EGF to the soft agar assay. These studies reporting TGF-like activity in nonneoplastic tissues and cells suggest that these tissue-derived growth factors may play a role in normal cell proliferation as well as neoplastic transformation (3, 12, 14). It has been shown recently that MSV-transformed cells contain, in addition to a TGF that binds to the EGF receptor (SGF), a separate TGF that requires EGF for stimulation of colony formation by NRK cells (13). Data have been presented indicating that the synergistic action of both types of TGF may be required for full expression of the transformed phenotype (1). The present study was undertaken to determine whether freshly excised human malignant neoplasms contain TGF-like activity and, if so, to compare this activity with any that might be present in human benign tumors and nonneoplastic tissues. Acid-ethanol extracts of 12 freshly excised human neoplasms and 2 nonneoplastic tissues were examined for TGF-like activity. All extracts stimulated the formation of progressively growing colonies in soft agar by nontransformed AKR-2B and/or NRK cells. The data provide further evidence that TGF-like polypeptides are not restricted to neoplastic tissues and that multiple forms of TGFs may be present within the same tissue. A complex interaction of multiple endogenous growth factors in neoplasia is suggested.

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MATERIALS AND METHODS

Tumor Specimens. Solid human malignant and benign neoplasms and nonneoplastic tissues removed at surgery were immediately frozen in liquid nitrogen and stored at -70° until used for extraction. A modification published previously (12) of the acid-ethanol extraction procedure used by Roberts et al. (15) was used to extract the tumors. The extracts were then dialyzed extensively against 1% acetic acid, lyophilized to dryness, and stored at -20°. Protein was estimated using a dye-binding assay (2).

Molecular Sieve Chromatography. The lyophilized dialysate from the crude tumor extracts was dissolved in approximately 30 ml of 1 M acetic acid and centrifuged at 1000 x g for 30 min (12). The supernatant was then applied to a 5 x 90-cm column of Bio-Gel P-60 equilibrated with 1 M acetic acid. The column was eluted with 1 M acetic acid at a flow rate of 30 ml/hr at room temperature with approximately 10-ml fractions being collected. The absorption of each fraction was determined at 280 nm, and aliquots of fractions were lyophilized for determination of specific activity.

Soj Soft Agar Assay. Soft agar assays were performed using nontransformed AKR-2B or NRK cells placed in purified agarose (Sea Plaque; Marine Colloids Division, FMC Corp., Rockland, Maine). Agar plates were prepared in 35-mm Petri dishes (Falcon No. 3001; Falcon Labware Division, Oxnard, Calif.) by first applying a 1 ml layer of 0.8% agarose in McCoy's Medium 5a containing 10% FBS. After the bottom layer had solidified, a top layer of 1 ml containing 0.4% agarose in medium with 10% FBS was added along with 7.5 x 10^3 mouse AKR-2B (9) or rat NRK (4) cells and the appropriate concentrations of protein from the different crude extracts, chromatography fractions, or pooled fractions. The plates were incubated at 37° in a humidified atmosphere of 5% CO2 and 95% air for 7 to 14 days. Colonies were quantitated using a Bausch and Lomb Omnimcon Feature Analysis Stem Model III. Colonies greater than 60 µm were scored as positive.

Competition for 125I-labeled EGF Binding to EGF Receptor. The 125I-labeled EGF radioreceptor assay was performed as described previously (8) using the A431 human squamous cell carcinoma line (4). This assay, 50% competition was obtained with approximately 0.5 ng of unlabeled EGF per ml (8). EGF, purified from male mouse salivary glands by the methods of Savage and Cohen (17), was labeled with 125I as described previously (16). The A431 cells were subcultured in 6-well plates (35-mm diameter, No. 3506; Costar, Cambridge, Mass.) at a density of 2.5 x 10^5 cells/well in McCoy's Medium 5a containing 10% FBS. The plates were incubated overnight. The binding assay was then performed as described previously (16) with different concentrations of the potential inhibitor incubated concurrently.

Characterization of TGF by Chemical and Physical Treatments. One-ng portions of the crude extract were dissolved in 1 ml of Dulbecco's phosphate-buffered saline, pH 7.2, and tested for sensitivity to trypsin, dithiothreitol, and heat. One aliquot was treated with trypsin (50 µg/ml) (crystalline trypsin, type 3; Worthington Biochemicals, Freehold, N. J.) for 2 hr at 37°. The reaction was stopped by the addition of soybean trypsin inhibitor (100 µg/ml) (Sigma Chemical Co.). The control sample was treated concurrently with trypsin (50 µg/ml) and soybean trypsin inhibitor (100 µg/ml) for 2 hr at 37°. The trypsin-soybean trypsin inhibitor mixture was preincubated for 30 min at room temperature before the addition of the sample. Another sample was subjected to a final heat treatment in a 56° water bath for 3 min and in boiling water for 3 min. After the above treatments, each sample was brought to 4 ml by the addition of Dulbecco's phosphate-buffered saline and dialyzed for 72 hr with 5 changes of 50 volumes of 1% acetic acid. Each sample was then lyophilized, dissolved in complete McCoy's Medium 5a containing 10% FBS, sterilized by filtration through 0.45-µm membrane filters (Millipore), and tested for stimulation of colony formation in the soft agar assay.

RESULTS

Colony-stimulating Activity in Malignant Neoplasms. Acid-ethanol extracts of 9 solid human malignant neoplasms removed at surgery were tested in varying amounts from 10 to 1000 µg/ml for their ability to stimulate AKR-2B and/or NRK cells to form colonies in soft agar. In all cases, a correlation between protein concentration and enhancement of the size and number of colonies formed was apparent; an example is presented in Chart 1. A survey of the colony stimulation observed using crude protein extract from each of the specimens (1.0 mg/ml) is shown in Table 1. Colony-stimulating activity was present in each of the specimens tested and did not vary consistently with the different types of neoplasms (i.e., carcinomas, sarcomas, and lymphoma). The amount of activity did vary with the individual specimens and with the indicator cell used (Table 1).

Chemical and Physical Treatments. Crude tumor extracts from the fibrosarcoma were subjected to various physical and chemical treatments (Table 2). The activity was stable to heat (56° for 30 min or 100° for 3 min) but was completely destroyed by trypsin. The trypsin inactivation was partially prevented when soybean trypsin inhibitor was preincubated with trypsin prior to adding the sample. Dithiothreitol also completely destroyed the colony-stimulating activity. These tests suggest that the activity is due to a heat-stable polypeptide with disulfide bonds.

Molecular Sieve Chromatography. Five of the tumor extracts (see Table 1, Specimens 3, 5, 7, 8, and 9) had sufficient material to be further characterized by molecular sieve chromatography.
20,000 range, and the NRK cells responded uniquely to a factor obtained with the same Bio-Gel P-60 fractions which were di

in the M, 10,000 range. While the AKR-2B cells responded uniquely to a factor in the M, 14,000 to 16,000 range with both indicator cells, indicator cells. A peak of colony-stimulating activity was ob

vided into 2 aliquots and set up the same day with the 2 different

nated TGFn). This is best shown in Chart 3 where the data were

could be separated from NRK colony-stimulating activity (desig

cochromatographed with at least one peak of AKR-2B

peak of AKR-2B colony-stimulating activity above M, 20,000

phoma and fibrosarcoma extracts also showed an additional

lating activity occurred in the M, 12,000 to 18,000 range in alltumor extracts examined (Charts 2 to 4). The Hodgkin’s lym

sorbing material. One or more peaks of AKR-2B colony-stimu

ments, AKR-2B colony-stimulating activity (designated TGFa)

activity cochromatographed with at least one peak of AKR-2B

activity using the nontransformed NRK cells as indicator cells.

on Bio-Gel P-60. As illustrated in Chart 2A, the peak of AKR-2B

soft agar-stimulating activity from an adenocarcinoma of the

breast did not cochromatograph with the bulk of the A280-ab-

soft agar-stimulating activity from an adenocarcinoma of the

Table 1

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Tumor or tissue type</th>
<th>NRK</th>
<th>AKR-2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Malignant neoplasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Adenocarcinoma, ovary (metastatic)</td>
<td>1726b</td>
<td>394</td>
</tr>
<tr>
<td>2</td>
<td>Adenocarcinoma, colon (metastatic)</td>
<td>—c</td>
<td>1725</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosarcoma</td>
<td>—c</td>
<td>1327</td>
</tr>
<tr>
<td>4</td>
<td>Leiomyosarcoma, uterus</td>
<td>768</td>
<td>395</td>
</tr>
<tr>
<td>5</td>
<td>Hodgkin’s lymphoma, mixed cellularity</td>
<td>689</td>
<td>758</td>
</tr>
<tr>
<td>6</td>
<td>Adenocarcinoma, breast (metastatic)</td>
<td>647</td>
<td>727</td>
</tr>
<tr>
<td>7</td>
<td>Adenocarcinoma, breast (infiltrative)</td>
<td>662</td>
<td>103</td>
</tr>
<tr>
<td>8</td>
<td>Adenocarcinoma, breast</td>
<td>388</td>
<td>478</td>
</tr>
<tr>
<td>9</td>
<td>Adenocinoma, kidney</td>
<td>305</td>
<td>479</td>
</tr>
<tr>
<td>10</td>
<td>Benign neoplasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Fibroadenoma, breast</td>
<td>1600</td>
<td>1050</td>
</tr>
<tr>
<td>11</td>
<td>Leiomyoma, uterus</td>
<td>1800</td>
<td>600</td>
</tr>
<tr>
<td>12</td>
<td>Leiomyoma, uterus</td>
<td>2000</td>
<td>380</td>
</tr>
<tr>
<td>13</td>
<td>Nonneoplastic tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Kidney</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>14</td>
<td>Lung</td>
<td>710</td>
<td>40</td>
</tr>
</tbody>
</table>

Notes:

a The weights of the tissue samples ranged from 2.0 to 21.0 g with a mean of 12.1 g. The mean protein yield in the crude extracts was 11.2 mg/g of tissue with a range of 4.7 to 19.9 mg/g.

b Number of colonies greater than 60 μm in diameter per dish.

c Not done.

A peak of colony-stimulating activity was observed in the M, 14,000 to 16,000 range with both indicator cells, while the AKR-2B cells responded uniquely to a factor in the M, 20,000 range, and the NRK cells responded uniquely to a factor in the M, 10,000 range.

**Competition for 125I-EGF Binding to A431 Cells.** In 3 of the specimens, Bio-Gel P-60 fractions were tested for competition with 125I-EGF for binding to A431 cell membrane receptors (Specimens 5, 8, and 9). There was no EGF receptor-competing activity in any of the fractions from the adenocarcinoma of the breast (Chart 2A) or adenocarcinoma of the kidney (data not shown). The Hodgkin’s lymphoma P-60 fractions did show minimal competition for EGF receptor which appeared to cochromatograph with the TGFα peak (Chart 3). The significance of this very low level of competition is difficult to ascertain.

**EGF Potentiation of Colony-stimulating Activity.** Roberts et

(14) have shown that EGF (2 ng/ml) markedly enhances the NRK colony-stimulating activity extracted from a variety of non-neoplastic tissues. Similar enhancement of NRK colony-stimulating activity but not of AKR-2B colony-stimulating activity has been observed in extracts from human platelets (3). In the present study, EGF potentiation of TGF activity was tested with Bio-Gel P-60 fractions from extracts of an adenocarcinoma of the kidney and 2 adenocarcinomas of the colon.

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Table 2

**Characteristics of fibrosarcoma extract colony-stimulating activity**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Colonies/dish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>488</td>
</tr>
<tr>
<td>Trypsin (50 μg/ml for 2 hr at 37°)</td>
<td>6</td>
</tr>
<tr>
<td>Trypsin (50 μg/ml) plus soybean trypsin inhibitor (100 μg/ml) for 2 hr at 37°</td>
<td>114</td>
</tr>
<tr>
<td>Dithiothreitol (0.065 M in 0.1 M NH₄HCO₃, 1 hr at 20°)</td>
<td>14</td>
</tr>
<tr>
<td>Heat (56° for 30 min)</td>
<td>475</td>
</tr>
<tr>
<td>Heat (100° for 3 min)</td>
<td>422</td>
</tr>
</tbody>
</table>

Notes:

a The number of colonies per dish measuring greater than 60 μm as measured with a Bausch and Lomb Omnicon Feature Analysis Stem Model II.

b Crude protein extracts (1-mg aliquots) were treated as described in “Materials and Methods” and, after the indicated treatment, were tested for colony-stimulating activity using the nontransformed NRK cells as indicator cells.

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Chart 2. Bio-Gel P-60 chromatography of acid-ethanol extracts of adenocarcinomas of the breast. A, chromatography of 80 mg of protein from the acid-ethanol extract of Specimen 8 (Table 1), indicating absorbance at 280 nm (Δ), stimulation of colony formation by AKR-2B cells (○), and competition with 125I-EGF for binding to A431 cell membrane receptors (×); B, results from 130 mg of protein from the acid-ethanol extract of Specimen 7 (Table 1), showing stimulation of colony formation by AKR-2B (○) and NRK (□) cells. Every third fraction was tested for the listed activity using the whole fraction. The molecular weight markers used were: carbonic anhydrase (M, 29,000); RNase (M, 14,000); and insulin (M, 6,000).
TGFs in Human Neoplasms

Chart 3. Bio-Gel P-60 chromatography of 250 mg of protein from the acid-ethanol extracts of a Hodgkin’s lymphoma. Every third whole fraction was tested for stimulation of colony formation by AKR-2B (○) and NRK (●) cells and for competition with 

\[ ^{125}I - \text{EGF} \] for binding to A431 cell membrane receptors (×). The molecular weight markers are the same as those listed in the legend for Chart 2.

EGF (2 ng/ml) to the soft agar assay gave a 2- to 5-fold enhancement of activity in peaks of NRK-stimulating activity already present without EGF but did not cause the appearance of separate peaks which were not present in the absence of added EGF (data not shown).

Colony-stimulating Activity in Benign Neoplasms. As shown in Table 1, three benign tumors showed marked colony-stimulating activity for both the AKR-2B and NRK cells. This colony-stimulating activity increased with increasing concentrations of protein as illustrated for the fibroadenoma of the breast in Chart 5. This benign tumor extract was subjected to molecular sieve chromatography (Chart 6). In contrast to the extracts from the malignant tumors including adenocarcinomas of the breast, all of the TGFn activity was in the Mr 4,000 to 6,000 range instead of the apparent Mr 12,000 to 18,000 range observed for NRK-stimulating activity in malignant neoplasms. The apparently

Chart 4. Bio-Gel P-60 chromatography of 82 mg of protein from the acid-ethanol extracts from a fibrosarcoma. The stimulation by every other whole fraction of colony formation by AKR-2B and NRK cells is illustrated. The molecular weight markers are the same as those listed in Chart 2.

Chart 5. Dilution curve of colony stimulation by acid-ethanol extract of fibroadenoma of breast. The AKR-2B and NRK cells were tested for colony stimulation by the quantities of extract indicated.

Chart 6. Bio-Gel P-60 chromatography of 27.5 mg of protein from the fibroadenoma of breast. Every other whole fraction was tested for stimulation of colony formation of AKR-2B and NRK cells. The molecular weight markers are the same as those used in Chart 2.
and NRK cells. The molecular weight markers are the same as those used in Chart 1.

Specimen 12 (Table 1) was tested for stimulation of colony formation of AKR-2B factor-like substances detected in the present study are similar, all of the benign and malignant neoplastic tissue examined as well as the nonneoplastic tissue examined in the malignant tumors (Charts 6 and 7).

Colonystimulating Activity in Nonneoplastic Tissues. Freshly excised human kidney and lung were extracted and examined for colony-stimulating activity (Table 1). The maximum activity from the kidney tissue, which was the uninvolved tissue from which Specimen 9 (Table 1) was obtained, showed less activity than did extracts from the neoplastic tissues. The nonneoplastic lung tissue had less AKR-2B-stimulating activity in crude extracts than did the neoplasms, but TGF activity was in the same range as that observed for most of the malignant neoplasms. Bio-Gel P-60 chromatography of the kidney and lung extracts gave profiles of colony-stimulating activity very similar to that observed with most of the malignant tumor examined with TGFa and TGFnl activity being predominant (data not shown). The addition of 2 ng of EGF per ml to the soft agar assay gave a 2- to 3-fold enhancement of NRK colony stimulation (TGFnl activity).

DISCUSSION

The results of this study demonstrate the widespread occurrence in human tissues of growth factor-like polypeptides that stimulate several rounds of cell division in nontransformed mouse and rat cells in a soft agar assay. Such factors were present in all of the benign and malignant neoplastic tissue examined as well as in nonneoplastic kidney and lung tissue. The growth factor-like substances detected in the present study are similar, if not identical, to the TGFs described previously (4, 8, 11, 15). They are heat- and acid-stable low-molecular-weight polypeptides which stimulate the growth in soft agar of nontransformed anchorage-dependent cells. They are unlike most of the better known growth factors described previously, such as EGF, fibroblast growth factor, platelet-derived growth factor, and insulin-like growth factors, since these latter compounds do not stimulate colony formation of either AKR-2B or NRK cells under the assay conditions used in this study (1, 13).

Three different types of TGF activity were detected in the human tissues examined in this study. TGFa, which stimulates colony formation by nontransformed mouse AKR-2B cells, was present in all of the specimens examined but in varying concentrations with generally lower quantities being present in the benign neoplasms and nonneoplastic tissues. Other studies from this laboratory on cultured mouse cells (20) indicate that this activity may be similar to the EGF-enhanced NRK colony-stimulating activity reported by Roberts et al. (14). The second type of TGF-like activity was TGFnl which selectively stimulates NRK cells in the absence of added EGF and chromatographed on a low molecular sieve column in the M, 12,000 to 20,000 range. This type of activity was detected in all of the malignant neoplasms examined by molecular sieve chromatography as well as in the nonneoplastic kidney and lung tissue. Very little of the TGFnl activity was present in the benign neoplasms. Instead, all 3 of the benign neoplasms examined contained TGFns activity which selectively stimulated colony formation by NRK cells in the absence of added EGF and chromatographed on the <6,000 molecular weight range. Previous reports of TGF activities that stimulate colony formation by NRK cells without EGF added to the soft agar assay include SGF isolated from medium conditioned by MSV-transformed mouse cells (4, 13) and factors produced by certain human cancer cells in culture (19). These factors, however, usually exhibit binding to the EGF receptor. In all of the specimens examined in the present study, no EGF receptor-competing activity cochromatographed with the TGFnl activity with the possible exception of the Hodgkin's lymphoma material (see Chart 3). TGFns activity was not tested for EGF receptor-competing activity. NRK colony-stimulating activity similar to the TGFnl observed in the present study has been found in chemically transformed mouse cells in culture (20) and in medium conditioned by human squamous cell carcinoma A431 cells (19).

In view of the previous reports of TGF activity in nonneoplastic mouse tissues (14), in mouse embryos (12, 21), and in human and bovine platelets and serum (3), it is not surprising that TGF activity was observed in the nonneoplastic tissue examined in the present study. The differences in the types of TGF activity between benign and malignant neoplasms, with the benign neoplasms containing only TGFns activity and not TGFnl and the malignant neoplasms containing TGFnl and not TGFns, were unexpected. The significance of this observation is obscure at the present time. The TGFnl and TGFns activities may be due to the same polypeptide(s) with the TGFnl representing aggregation or binding to a carrier protein.

Compounds with TGF activity may be present in nontransformed cells and yet play a role in the neoplastic transformation of these cells. The apparent quantity in tissue as detected by the methods used in the present study may not reflect the endogenous activity of these growth factor-like substances.
Their activity may be regulated by labile inhibitors which are inactivated by the relatively harsh extraction procedures used. Preliminary evidence for a heat-labile inhibitor of the TGFs activity in nonneoplastic human tissue has been obtained. The possible role of TGF inhibitors in regulating TGF activity is still under investigation in this laboratory. In addition, a cell which produces an endogenous growth factor may not be capable of responding to the factor. If the cell changes such that it can respond to the factor which it already produces and becomes autostimulatory, the cell would have a growth advantage and perhaps exhibit the neoplastic phenotype. Evidence for such changes occurring in mouse cells in culture in association with chemical transformation has been obtained (20). It is also possible that TGF-like compounds extracted from cells in tissues are not compounds which normally function in the control of cell proliferation but have other functions, as yet undetermined, and exhibit growth-promoting capabilities only fortuitously.

It is of considerable interest that multiple growth factor-like polypeptides can be detected in human neoplastic and nonneoplastic tissues. Three apparently different factors were detected in the present study, and Halper and Moses (6) have presented evidence for the presence of an additional separate factor from human tissues which selectively stimulates SW-13 human carcinoma cells. It is possible that normal tissues and cells contain a relatively large number of different growth factors which play an important role in normal growth and development and in the regulation of cell proliferation in the adult state. Changes in the production of or response to such factors could play a role in neoplastic transformation. However, demonstration of such a role for these endogenous factors in normal growth or neoplasia will require purification of the factors and a determination of the role they play in supporting growth of different types of cells in culture utilizing chemically defined media.

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