Human Mesothelioma Cells Produce Factors That Stimulate the Production of Hyaluronan by Mesothelial Cells and Fibroblasts

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ABSTRACT

The hyaluronan production by three human malignant mesothelioma cell lines and nine primary human mesothelial cell types was determined. The mesothelioma cell lines produced only minute amounts of hyaluronan (less than 0.1 pg/106 cells/48 h) whereas mesothelial cells synthesized large quantities of hyaluronan (10-72 pg/106 cells/48 h). Conditioned media from the mesothelioma cell lines were investigated for their ability to stimulate hyaluronan production by fibroblasts and mesothelial cells in vitro, and in all cases stimulatory effects were found. The factor(s) in the conditioned medium of the mesothelioma cell line Mero-25 that were responsible for hyaluronan stimulation were heat stable and partially trypsin resistant. The stimulatory activity was partially inhibited by an antiserum against platelet-derived growth factor and basic fibroblast growth factor. Our data suggest that the increased hyaluronan synthesis seen in patients with mesothelioma is due to the release of factors from mesothelioma cells that stimulate other cells to produce hyaluronan.

INTRODUCTION

Mesothelial cells of pleura, pericardium, and peritoneum are the progenitor cells of mesothelioma, a malignant tumor that has been associated with exposure to asbestos fibers (1, 2). It has been proposed that damage of mesothelial cell DNA is generated by oxygen free radicals from fiber-activated macrophages and is followed by the stimulation of growth by growth factors released by macrophages or the mesothelial cells themselves (3). NHM3 cells can be maintained in vitro in a rich medium supplemented with EGF and hydrocortisone, as described by Connell and Rheinwald (4). PDGF, TGF-β, fibroblast growth factor, and EGF have been found to be mitogenic for NHM cells (5, 6). In addition, NHM cells as well as mesothelioma cells express mRNA for TGF-β and secrete TGF-β (7, 8). Human malignant mesothelioma cell lines express higher levels of mRNAs for PDGF A-chain and PDGF B-chain than NHM cells, and PDGF-like activity was detected in conditioned medium from mesothelioma but not from mesothelial cells (7, 9). Based on these observations it has been suggested that autocrine stimulation involving different factors may have a role in the uncontrolled growth of mesotheliomas.

A common clinical finding in patients with malignant mesothelioma is the large amounts of hyaluronan found in their pleural effusions or ascites (10-12), and in their blood (13-15). Hyaluronan is a linear polysaccharide which consists of repeating N-acetylglucosamine and glucuronic acid disaccharide units. It is ubiquitously distributed in the body and has been assigned various physiological functions; hyaluronan networks exhibit osmotic and flow resistance properties that make it important in tissue water homeostasis. Furthermore, these networks exclude or retard other macromolecules regulating in this way the transport and distribution of plasma protein in the tissues (16). In addition to its physicochemical functions, hyaluronan is implicated in many biological processes. Hyaluronan has been suggested to have important roles, for instance in embryogenesis, cell growth, angiogenesis, and wound healing (16-20).

Hyaluronan is synthesized by a membrane bound enzyme, hyaluronan synthetase (21,22), through the addition of monosaccharides to the reducing end while the polysaccharide is extruded through the plasma membrane (23). The production of hyaluronan by cells in culture is stimulated by certain growth factors, such as PDGF, EGF, fibroblast growth factor, insulin growth factor I, and TGF-β (24, 25). The stimulation by PDGF is dependent on protein synthesis and most likely involves protein tyrosine phosphorylation (25, 26).

The aim of the present investigation was to study the mechanism behind the increased hyaluronan production in patients with malignant mesothelioma. A number of human mesothelioma-derived cell lines were analyzed for the production of hyaluronan. In contrast to normal mesothelial cells which produce large quantities of hyaluronan, the mesothelioma cell lines were found to synthesize only minute amounts of the polysaccharide. However, the mesothelioma cells produced factors that potently stimulated hyaluronan production in cultures of normal mesothelial cells and fibroblasts.

MATERIALS AND METHODS

Materials. Recombinant PDGF-AA and -BB (27) and the IgG fractions of rabbit antiserum recognizing PDGF-AA, PDGF-BB (28), or all PDGF isoforms (29) were from C-H. Heldin (Ludwig Institute for Cancer Research, Uppsala, Sweden). EGF was a gift from A. Thomason (Amgen, Thousand Oaks, CA). bFGF was purchased from Amersham International and IgG fractions of a rabbit anti-bFGF were from Sigma Immunochemicals. TGF-β was a gift from K. Miyazono (Ludwig Institute for Cancer Research) and IgG fractions of a rabbit anti-TGF-β were obtained from R & D Systems, Minneapolis, MN. Hydrocortisone, trypsin, and soybean trypsin inhibitor were obtained from Sigma. Nutrient mixture Ham’s F-10 and the other cell culture reagents were from Gibco, Paisly, United Kingdom. [3H]Thymidine was obtained from Amersham (90 Ci/mmol).

Culture Conditions. Primary cultures of NHM cells were initiated either from human biopsies from the anterior or medial part of the pleural cavity as described by Heldin et al. (26) or from pleural effusions (30). The human malignant mesothelioma cell lines Mero-25, Mero-14, Mero-82 were established by Versnel et al. (30). The TM-2 cell line which was spontaneously transformed was established by Langerak et al. (31). Mesothelioma cells and human foreskin fibroblasts (AG1518, obtained from the Human Mutant Repository, Camden, NJ) were maintained in Ham’s F-10 medium supplemented with 10% fetal calf serum, 4 mM L-glutamine, 100 IU/ml penicillin, and 100 μg/ml streptomycin. NHM cells were grown in the same medium plus 10 ng/ml EGF and 0.4 μg/ml hydrocortisone.

Preparation of Conditioned Medium. Confluent cultures of Mero-25 cells or NHM cells (PL 1U), grown in 175-cm2 Falcon bottles containing F-10 medium with 10% FCS (plus 10 ng/ml EGF and 0.4 μg/ml hydrocortisone) for PL 1U, were washed once with serum-free medium and then incubated about 16 h in serum-free medium. Both these media were discarded. To obtain Mero-25 or PL 1U conditioned medium, fresh serum-free F-10 medium (50 ml) was then added and cells were cultured for different periods of time.

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2 To whom requests for reprints should be addressed.

3 The abbreviations used are: NHM, normal human mesothelial; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; bFGF, basic fibroblast growth factor; FCS, fetal calf serum.
Conditioned medium was concentrated 10-fold using Amicon filters (Spectrapor, YM 2 membrane with a molecular weight cutoff of 1000); the concentration was added at 50% concentration in relation to culture media, or as indicated, to the culture media of quiescent target cells (fibroblasts or mesothelial cells). Quiescent cells were obtained after culturing the cells in serum-free medium for 24 h without EGF and hydrocortisone. Nonconditioned F-10 medium was treated in the same way as Mero-25 conditioned medium and used as a control.

**Determination of Hyaluronan Synthesis.** Unless otherwise specified, NHM cells and human foreskin fibroblasts were plated into 12-well Costar tissue culture dishes (about 50,000 cells/well), in F-10 medium containing 10% FCS, 4 mg/l-glutamine, 100 IU/ml penicillin, and 100 μg/ml streptomycin, plus 10 ng/ml EGF and 0.4 μg/ml hydrocortisone for NHM cells. Twenty-four h later, medium was changed to serum-free medium deprived of EGF and hydrocortisone. After about 24 h, the quiescent cells in a final volume of 500 μl received fresh serum-free F-10 medium, Mero-25-conditioned medium (50% final concentration), PDGF (50 ng/ml), or BF-1 (3 ng/ml) in the absence or presence of 80 μg/ml anti-PDGF IgG or anti-BFGF IgG. At different incubation times cultures were tested for the amount of hyaluronan secreted into the medium with a commercial kit (hyaluronan test 50; Pharmacia, Uppsala, Sweden). Direct measurement of hyaluronan synthetase activity in membrane preparations of NHM cells and mesotheliomas was performed according to the method of Heldin et al. (26). Briefly, about 2 × 10^6 cells/150 × 25-mm tissue culture dishes were harvested in 50 ml 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, pH 7.0, containing 0.24 μC sulfate, 2 μl EDTA, 1 μl dithiothreitol, and 10 μg of leupeptin/ml. After three cycles of freezing at −70°C followed by thawing and Dounce homogenization, the cell homogenates were centrifuged at 95,000 × g for 20 min. The cell pellets were resuspended in the above buffer and tested for hyaluronan synthetase activity; 400 μM UDP-N-acetylglucosamine, 20 μM UDP-[14C]glucuronic acid, 6 mM MgCl₂, and 100–500 μg of membrane protein were incubated at 37°C for 1 h. The reaction was terminated by adding 10 μl of 20% sodium dodecyl sulfate, following heating of the samples at 95°C for 3 min. The synthesized [14C]-labeled hyaluronan was obtained in the void volume of a Sephadex G-50 Superfine column (12.5 × 1 cm).

**Determination of Growth-promoting Activity in Mero-25-conditioned Medium.** NHM cells and human foreskin fibroblasts were seeded at 25,000 cells/cm² Costar well in 1 ml medium. After 24 h, the medium was removed and the cells were washed once. Cell cultures were then starved in F-10 medium supplemented with 0.5% FCS and antibiotics for 2 days. At this time fresh F-10 medium containing 0.5% FCS was added together with test samples including Mero-25 or NHM cell-conditioned medium, concentrated F-10 medium (at a final concentration of 50% in the culture medium), 50 ng/ml PDGF-BB, or 10% FCS. Twenty-four h later the cells were exposed for an additional 8 h to 2 μCi of [3H]thymidine/well. The medium was then removed and cell cultures were incubated with 5% (v/v) trichloroacetic acid for 20 min at 4°C. Following two washes with water, the precipitated DNA was dissolved in 200 μl of 1 × NaOH for 20 min at room temperature and then subjected to liquid scintillation counting.

**Initial Characterization of the Hyaluronan-stimulating Factor(s).** Conditioned medium from the mesothelioma cell line Mero-25 was prepared as described above and then treated with 50 μg/ml trypsin at 37°C for 2 h. A 2-fold molar excess of soybean trypsin inhibitor was then added and the mixture was incubated for an additional 30 min at 37°C. The trypsin-treated conditioned medium was then analyzed for hyaluronan-stimulating activity. As a control for the trypsin treatment, a sample was incubated for 2 h at 37°C with trypsin that had been preincubated with soybean trypsin inhibitor for 30 min at room temperature; the hyaluronan-stimulating activity was similar to that of untreated Mero-25-conditioned medium (not shown). Conditioned media were also tested for their heat sensitivity by incubation at 56°C for 30 min or at 80°C for 10 min; samples were then analyzed for hyaluronan-stimulatory activity.

**RESULTS**

In order to investigate possible reasons why patients with mesothelioma have high concentrations of hyaluronan in their pleural or peritoneal fluids, the amount of hyaluronan produced by human malignant mesothelioma cell lines and NHM cells was determined (Table 1). The amount of hyaluronan released by Mero-25, Mero-14, Mero-82, and TM-2 cells in culture medium containing 10% FCS was 100-fold lower compared to primary cultures of NHM cells. The dramatic difference in the amount of hyaluronan released into the culture medium between mesothelioma and mesothelial cells is not due to an entirely inactive hyaluronan synthetase in the transformed cells; hyaluronan synthetase activity in plasma membrane preparations of mesothelioma cells was only about 3-fold lower compared to NHM cells (Table 1). These results prompted us to investigate the possibility that the high levels of hyaluronan found in patients with mesothelioma may reflect the stimulatory effect of factors produced by mesothelioma cells on hyaluronan synthesis by mesothelial cells and fibroblasts.

The stimulatory effect of conditioned medium from the mesothelioma cell line Mero-25 on hyaluronan production in quiescent human fibroblasts (Fig. 1a) and human mesothelial cells (Fig. 1b) was tested. A concentration of 50% of 10-fold concentrated conditioned medium in relation to culture medium (v/v) was sufficient to induce an almost maximal effect in mesothelial cells and 70% of the maximal effect in fibroblasts. The results indicate that factors stimulating hyaluronan production in normal mesothelial cells and fibroblasts are produced by mesothelioma cell lines in fairly large quantities. The stimulation of hyaluronan synthesis was time dependent (Fig. 2). Furthermore, the amount of stimulatory activity in medium conditioned by Mero-25 cultures was higher in medium conditioned for 72 h than in media conditioned for 48 h or 24 h; control medium was negative (Fig. 2). Conditioned media from the mesothelioma cell lines Mero-14 and Mero-82 had hyaluronan-stimulating effects on fibroblasts and mesothelial cells similar to that of the conditioned medium from Mero-25 (results not shown).

It is known that many mesothelioma cell lines produce PDGF (7–9). Since PDGF has been found to stimulate hyaluronan synthesis by human fibroblasts and NHM cells (24, 26, 32), we investigated

**Table 1** Hyaluronan synthesis by NHM and mesothelioma cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Origin</th>
<th>Hyaluronan secreted into culture medium (μg/10^6 cells)</th>
<th>Hyaluronan synthetase activity (pmol/h/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meso-25</td>
<td>Tumor</td>
<td>&lt;0.1</td>
<td>11</td>
</tr>
<tr>
<td>Mero-14</td>
<td>Effusion</td>
<td>&lt;0.1</td>
<td>14</td>
</tr>
<tr>
<td>Mero-82</td>
<td>Tumor</td>
<td>&lt;0.1</td>
<td>21</td>
</tr>
<tr>
<td>TM-2 a</td>
<td>Effusion</td>
<td>&lt;0.1</td>
<td>9</td>
</tr>
<tr>
<td>Primary cultures of NHM cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 1U</td>
<td>Biopsy</td>
<td>10.0</td>
<td>70</td>
</tr>
<tr>
<td>P1 10UA</td>
<td>Biopsy</td>
<td>12.6</td>
<td>n.d.</td>
</tr>
<tr>
<td>P1 10UC</td>
<td>Biopsy</td>
<td>10.2</td>
<td>n.d.</td>
</tr>
<tr>
<td>P1 11U</td>
<td>Biopsy</td>
<td>15.1</td>
<td>53</td>
</tr>
<tr>
<td>P1 18MT</td>
<td>Biopsy</td>
<td>18.6</td>
<td>n.d.</td>
</tr>
<tr>
<td>P1 19MT</td>
<td>Biopsy</td>
<td>29.5</td>
<td>52</td>
</tr>
<tr>
<td>P1 20AT</td>
<td>Biopsy</td>
<td>71.9</td>
<td>113</td>
</tr>
<tr>
<td>PLIP</td>
<td>Effusion</td>
<td>n.d.</td>
<td>91</td>
</tr>
<tr>
<td>NM-14</td>
<td>Effusion</td>
<td>n.d.</td>
<td>189</td>
</tr>
</tbody>
</table>

**Fibroblasts**

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>AG 1518</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>39</td>
</tr>
</tbody>
</table>

*One × 10^6 cells from different cell types were incubated for 48 h in F-10 medium containing 10% FCS and antibiotics in a final volume of 15 ml. Samples were taken from the medium and analyzed for hyaluronan content as described in "Materials and Methods." The values represent duplicate determinations of hyaluronan content into cell culture medium. The interassay variation was less than 10%.

* Membrane preparations from different cell types were tested for their hyaluronan synthetase activity (pmol of 14C-glucuronic incorporated into newly synthesized hyaluronan/hmg of protein).

* TM-2 is a cell line spontaneously transformed in vitro.

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MESOTHELIOMA-SECRETED FACTORS STIMULATE HYALURONAN SYNTHESIS

Whether antibodies against PDGF were able to neutralize the stimulatory effect on the hyaluronan synthesis found in the conditioned medium. As shown in Fig. 3, the major part of the hyaluronan-stimulatory activity of Mero-25-conditioned medium was not neutralized by the antibodies recognizing all isoforms of PDGF, whereas these antibodies inhibited the stimulation by PDGF-BB. Similar experiments performed with a mixture of antibodies against PDGF-AA and PDGF-BB gave similar results (data not shown). Thus, some of the stimulatory effect on hyaluronan synthesis may be due to PDGF, while the major part of the stimulatory activity is due to other factor(s). Furthermore, previous studies have shown that bFGF and TGF-β stimulate the synthesis of hyaluronan (24). Therefore, we investigated whether antibodies against bFGF could neutralize the stimulatory effect of conditioned medium from Mero-25 cells. A part of the activity was neutralized by antibodies against bFGF (Fig. 3). This effect was more profound in mesothelial cells (Fig. 3b) than on fibroblasts (Fig. 3a). According to Gerwin et al. (7) mesothelioma and NHM cells secrete both latent and active forms of TGF-β. However, antibodies against TGF-β did not neutralize the hyaluronan-stimulatory effect of Mero-25 cell-conditioned medium (data not shown).

Moreover, acidification of the conditioned medium which activates the latent forms of the TGF-β did not lead to an increase in the hyaluronan-stimulatory activity (data not shown). We conclude that part of the stimulatory activity is due to PDGF and bFGF but that other factors also are likely to contribute.

To further characterize the nature of the hyaluronan-stimulating activity we investigated its susceptibility to trypsin and heat. Part of the hyaluronan-stimulating activity in the conditioned Mero-25 medium was destroyed by trypsin (50 μg/ml) when tested on NHM cells or fibroblasts (Table 2). Heating of the conditioned medium at 56°C for 30 min or at 80°C for 10 min inhibited only a small amount of the hyaluronan-stimulating activity for NHM cells whereas the stimulatory activity for fibroblast cultures was not at all sensitive to heat (Table 2). Thus the hyaluronan-stimulating activity is fairly heat stable.

In order to compare the stimulatory activity of medium conditioned by Mero-25 on hyaluronan synthesis with that on cell growth, the ability of the conditioned medium to stimulate [³H]thymidine incorporation in quiescent mesothelial cells and fibroblasts was investigated. The conditioned medium from Mero-25 cells possessed mitogenic activity toward NHM cells (PL 1U) and human fibroblasts with 6- and 35-fold stimulations, respectively, of the [³H]thymidine incorporation (data not shown). Also medium conditioned by the PL 1U cells contained growth-promoting activity for mesothelial cells themselves and fibroblasts.

Fig. 1. Stimulation of hyaluronan production by conditioned medium from Mero-25 cells. Medium conditioned for 72 h by the human mesothelioma-derived cell line Mero-25 (●) was added at different concentrations (v/v) to (a) quiescent human fibroblasts (AG 1518) and (b) human mesothelial cells (PL 1U). As a control, F-10 medium treated in the same way as conditioned medium from Mero-25 cells, was tested (○). Forty-eight h later samples were tested for hyaluronan secreted into the culture medium. Data are from a representative experiment; values are the average of two separate determinations ± variation (bars).

Fig. 2. Stimulation of hyaluronan production by medium from Mero-25 cells conditioned for various time periods. Medium was conditioned by Mero-25 cells for 24 h (●), 48 h (■) and 72 h (▲). It was then added, at a final concentration of 50%, to quiescent cultures of (a) fibroblasts (AG 1518) and (b) mesothelial cells (PL 1U). The amount of hyaluronan secreted into the culture medium was determined after different time periods. As a control, F-10 medium treated in the same way as conditioned medium from Mero-25 cells, was tested (○). Data illustrate a representative experiment; values are the average of three separate determinations; bars, SEM.
bFGF IgG and combinations thereof was determined. As a control, F-10 medium was


cells, 50 ng/ml PDGF-BB, 3 ng/ml bFGF, 80 ng/ml anti-PDGF IgG, or 80 ng/ml anti-


determinations from a representative experiment ± variation.


Forty-eight h after addition of the factors, samples were taken from the media and

and (b) mesothelial cells (PI IU) in response to medium conditioned for 72 h by Mero-25

Table 2. Trypsin and heat susceptibility of the hyaluronan-stimulatory activity of Mero-25 cell-conditioned medium

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hyaluronan production (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control medium</td>
<td>Mesothelial cells</td>
</tr>
<tr>
<td>Untreated</td>
<td>0</td>
</tr>
<tr>
<td>Mero-25-conditioned medium</td>
<td>Untreated</td>
</tr>
<tr>
<td>Mero-25-conditioned medium, treated with trypsin</td>
<td>75 ± 1.0</td>
</tr>
<tr>
<td>Mero-25-conditioned medium, treated at 56°C for 30 min</td>
<td>91 ± 5.0</td>
</tr>
<tr>
<td>Mero-25-conditioned medium, treated at 80°C for 10 min</td>
<td>80 ± 0.5</td>
</tr>
</tbody>
</table>

NMM cells and fibroblasts were plated at 5 x 10⁴ cells/well in the presence of Mero-25 cell-conditioned medium (at a final concentration of 50% compared to culture medium) untreated, trypsin treated, or heat treated. The effect on hyaluronan production of F-10 medium treated in the same way as Mero-25 cell-conditioned medium was used as control. Data represent mean of duplicates of a representative experiment ± variation.

DISCUSSION

We show in this study that whereas human mesothelioma cells produce only minute quantities of hyaluronan, they secrete factors that potentely stimulate the production of hyaluronan by normal mesothelial cells and fibroblasts. A part of the activity, but not all, could be ascribed to PDGF and bFGF. NHM cells have been shown to respond mitogenically to a wide spectrum of factors, e.g., bFGF, EGF, TGF-β, and PDGF (5, 6). Furthermore, for sustained cell multiplication, NHM cells need hydrocortisone, insulin, transferrin, and high density lipoproteins. Many factors that stimulate hyaluronan synthesis also stimulate DNA synthesis. In the present study we found that Mero-25 cell-conditioned medium, which stimulated hyaluronan synthesis in both NHM cells and fibroblasts, also stimulated DNA synthesis. However, further studies are needed to determine whether the same or different factors in the conditioned media from Mero-25 cells or mesothelial cells are responsible for the proliferative and hyaluronan-stimulatory activities. Slight differences were observed in the effect of the conditioned medium on the stimulation of hyaluronan in mesothelial cells and fibroblasts. This is likely to be due to the fact that different factors are involved which have differential effects on the two cell types.

In patients with malignant mesotheliomas high levels of hyaluronan are often found. During tumor invasion, changes of the tumor extracellular matrix occur due to proteolytic cleavage of structural proteins. A more hydrated extracellular matrix enriched in hyaluronan, and resembling an early embryonic matrix, is formed (33-35). It is known that many tumors in vivo are enriched in hyaluronan whereas the isolated tumor cells synthetize very low amounts of hyaluronan, suggesting that production of factors by the tumor cells which stimulate hyaluronan synthesis in the host tissue is common in different tumor types (36). Additionally, cocultures of several human carcinoma cell lines and normal human fibroblasts, as well as tumor extracts, possess hyaluronan-stimulatory activity (36). Our findings extend these observations and suggest that the high concentration of hyaluronan found in patients with mesothelioma is due to factor(s) secreted by mesothelioma cells themselves, acting in a paracrine way to stimulate hyaluronan production in neighboring fibroblasts and mesothelial cells.

It remains to purify and characterize the mesothelioma factors responsible for the stimulation of hyaluronan production. Detailed knowledge of these factors is of importance for the understanding of the regulation of hyaluronan synthesis by normal or transformed cells and their possible role in the development of mesothelioma tumors.

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REFERENCES

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