Normal Human Mesothelial Cells and Mesothelioma Cell Lines Express Insulin-like Growth Factor I and Associated Molecules

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ABSTRACT

Insulin-like growth factor (IGF) I has important growth regulatory functions in normal growth and development. IGF-I is also a mitogen for a number of cancer cell lines; however, its autocrine effect has not been well established. In this study, the expression of IGF-I, its receptor, and its major serum-binding protein were examined in 5 normal human mesothelial (NHM) cell samples and 11 pleural mesothelioma cell lines. All NHM cells and mesothelioma cell lines expressed IGF-I, IGF-binding protein 3 (IGFBP-3), and IGF-I receptor mRNA by either Northern blot or reverse transcription polymerase chain reaction analysis. IGF-I (0.136 ± 0.024 ng/ml, mean ± SEM) and IGFBP-3 (15.9 ± 1.3 ng/ml) proteins were readily detected in the conditioned medium of mesothelioma cell lines but were not greater than corresponding measurements in that of NHM cells (IGF-I, 0.120 ± 0.080 ng/ml; IGFBP-3, 15.9 ± 1.3 ng/ml). Exogenous recombinant IGF-I stimulated cell proliferation of NHM cells, demonstrating the presence of a functional IGF-I receptor. Our results suggest that IGF-I may function as an autocrine growth stimulus in normal proliferating mesothelial cells, which may contribute to their malignant transformation.

INTRODUCTION

Malignant mesothelioma has a unique association with asbestos exposure with approximately two-thirds of cases having an occupational or environmental contact with asbestos (1, 2). These rare tumors arise from mesothelial cells which are of mesodermal origin and line body cavities, including the pleura and peritoneum. All asbestos fiber types have been implicated in the pathogenesis of mesothelioma, but epidemiological studies suggest a risk gradient with amphiboles, especially crocidolite (1, 2). NHM cells are exquisitely sensitive compared to human bronchial epithelial cells or fibroblasts to the cytotoxic and clastogenic effects of asbestos fibers (3, 4). The mechanisms by which asbestos fibers transform normal mesothelial cells have yet to be defined; however, the altered expression of growth factors is prominent in this process and enhances tumor progression.

Exogenous growth factors stimulate the proliferation of normal diploid cells in culture. Cultured malignant cells often demonstrate independence from exogenous growth factors, a characteristic of malignant cells resulting from the autocrine production of growth factors (5). Human mesothelioma cell lines have been reported to express both PDGF-A and -B chain genes at higher levels than cultured normal mesothelial cells (6, 7), express the β-receptor whereas normal mesothelial cells express the α-receptor (8), and secrete PDGF-like mitogenic activity into conditioned medium (6, 9). Although PDGF is mitogenic for NHM cells (10), this has yet to be demonstrated for malignant mesothelioma cells (11). However, the tumorigenic conversion by overexpression of PDGF-A chain of an SV40 T-antigen-immortalized nontumorigenic human mesothelial cell line implicates a role for the PDGF-A chain in mesothelial cell tumorigenesis (9).

NHM cells respond mitogenically to a number of growth factors including epidermal growth factor, transforming growth factor-β, PDGF-AB heterodimer and -BB homodimer, fibroblast growth factor, interleukin-1α and -β, interferon-γ, and interferon-β (10, 12–14). Growth factor responsiveness results in increased mesothelial cell division which would predispose these cells to asbestos-induced aneuploidy. Chrysotile-exposed cells in anaphase have been shown to contain significant increases in the number of cells with anaphase abnormalities including lagging, bridging, and sticky chromosomes (15). Asbestos fibers were found in mitotic cells to interact directly with chromosomes (16). Asbestos-induced aneuploidy probably results from the physical disruption by asbestos fibers of chromosomal segregation during mitosis (15).

IGF-I acts synergistically with PDGF in promoting mesenchymal cell proliferation (17). IGF-I-mediated growth stimulation of tumor cells has been reported for several neoplastic epithelial and mesenchymal cell types (18–30). Because mesotheliomas are rare tumors of mesodermal origin with both epithelial and mesenchymal cell features, we hypothesized that IGF-I may play an important role in mesothelial cell tumorigenesis.

IGF-I, a 70-amino acid basic polypeptide, is produced from the human IGF-I gene on chromosome 12 that contains five exons transcribed by alternate splicing to two mRNA species. The two precursor peptides, IGF-IA (153 amino acids) and IGF-IB (195 amino acids), have identical amino-terminal amino acids but different carboxyl-terminal extensions (31, 32). The signal for IGF-I is mediated by the IGF-I receptor similarly to the insulin receptor composed of 2 α (M, ~135,000) and 2 β (M, ~90,000) subunits connected by disulfide bonds in a functional β-α-β-heterotetrameric receptor complex. When IGF-I binds to the extracellular domain, it stimulates intracellular tyrosine kinase activity producing β subunit autophosphorylation and presumably cytoplasmic substrates of an IGF-I-specific signal transduction pathway (33, 34). The actions of IGFs in tissues are modulated by IGFBPs. Recently, six distinct IGFBPs were isolated and their cDNAs cloned (35–48). IGFBP-3 is the major BP in human serum for IGF-I. The principal effect of IGFBP-3 in vitro is to inhibit the action of IGF-I, although potentiation of IGF-I action has been demonstrated as well under different culture conditions (49–52).

To investigate the role of IGF molecules in malignant mesothelioma, we evaluated the effect of recombinant IGF-I on mesothelial cell growth, the mRNA expression of these IGF genes in normal and malignant human mesothelial cells, and their secretion of IGF-I and IGFBP-3 peptide into conditioned medium. Our results suggest that IGF-I may function as an autocrine growth stimulus in normal proliferating mesothelial cells, which may contribute to their malignant transformation.

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3 The abbreviations used are: NHM, normal human mesothelial; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; BP, serum-binding protein; IGFBP, insulin-like growth factor-binding protein; IGF-IR, insulin-like growth factor I receptor; DMEM, Dulbecco’s modified Eagle’s medium; cDNA, complementary DNA; SDS, sodium dodecyl sulfate; RT, reverse transcription; PCR, polymerase chain reaction.
MATERIALS AND METHODS

Cells and Culture Conditions. Eleven malignant mesothelioma cell lines were isolated and developed from pleural effusions, biopsy, or resected material from patients with cytologically, histologically, immunohistochemically, and ultrastructurally confirmed malignant pleural mesotheliomas. Cyto genetic studies on short-term chromosome harvests of tumors demonstrated aneuploidy. Tissue specimens were minced and incubated in growth medium consisting of a 1:1 composition of DMEM and Ham’s F12 medium (Whittaker Bioproducts, Walkersville, MD), supplemented with 10% fetal calf serum (GIBCO BRL, Grand Island, NY), penicillin (0.1 mg/ml), and streptomycin (0.1 mg/ml). Cell cultures were incubated at 37°C in a humidified atmosphere of 5% CO₂ for 14 days to achieve 75% confluence. Mesothelioma pleural effusions were prepared by initially centrifuging at 1000 X g for 10 min. of near-confluent cultures were dissociated using trypsin and either expanded by inoculating 2 x 10⁵ cells/T15 flask, cryopreserved, or used in experimental protocols. Two normal human mesothelial cell lines, LP-3 and LP-9, were purchased from the National Institute on Aging Cell Repository (Camden, NJ). Normal mesothelial cells were also isolated from transudative pleural effusions obtained from patients (n = 3) with congestive heart failure and no history of malignancy and prepared as described above. These cells were cytologically identified as mesothelial cells and expressed vimentin and cytokeratins by immunocytochemistry. The cells were cultured in the same growth medium supplemented with epidermal growth factor (10 ng/ml; Collaborative Research, Bedford, MA). Human non-small cell lung cancer cell lines (SK-MES-1, A549, and Calu-3) were purchased from American Type Culture Collection (Rockville, MD) and cultured in DMEM and Ham’s F12 supplemented with 10% fetal calf serum and antibiotics as above.

Cell Growth Assay. Normal mesothelial cells (1 x 10⁵) were placed into 96-well plates in serum-free medium and incubated at 37°C in a 5% CO₂ atmosphere. Within the first 24 h after plating, the medium was changed to either serum-free medium alone or that containing additives: recombinant human IGF-I (100 ng/ml; a generous gift from Ciba-Geigy, Suffern, NY), recombinant human PDGF-AB (10 ng/ml; Upstate Biotechnology, Inc., Lake Placid, NY), or 10% FCS. The cells were allowed to grow for 3 days. The plates were removed from the incubator, and the medium was rapidly decanted. The cells were fixed for 15 min with 10% formalin in 9% acetic acid-0.1 M sodium acetate buffer. The cells were then stained with a solution of 0.5% naphthol blue black (Aldrich Chemical Co., Milwaukee, WI) in 9% acetic acid sodium acetate buffer. The cells were then washed with H₂O₂ and the dye was eluted by adding 50 msi NaOH (150 µl/well). Absorbance of each well was read at 630 nm in a Dynatech Minireader 5000 (53).

IGF-1 and IGF-FBP-3 Radioimmunoassay. Cells were seeded into T15 flasks and cultured until approximately 75% confluent. The monolayers were washed twice with phosphate-buffered saline, and medium was replaced with 10 ml of serum-free medium. After a 24-h incubation, the medium was collected and centrifuged at 1000 x g for 5 min, and the supernatant was stored at -70°C. Immunoreactivity for IGF-1 and IGF-FBP-3 was determined from conditioned media by radioimmunoassay as previously described (54).

Northern Analysis. RNA was extracted from subconfluent cultures of mesothelial cell lines using a modified method of Chirgwin et al. (55). Polyadenylated RNA was selected over oligo(dT)-cellulose column chromatography, separated by electrophoresis in a 1% agarose-6% formaldehyde denaturing gel, transferred onto nylon filters (BA 85; Schleicher & Schuell) and baked at 80°C for 2 h. The filters were incubated at 42°C for 2-4 h in prehybridization buffer (50% formamide-5X SSPE-5X Denhardt’s reagent-2.5% herring sperm DNA-0.1% SDS) and hybridized to cDNA probes labeled with [35S]dCTP (3000 Ci/mmol; New England Nuclear, Boston, MA) to a specific activity of >1 x 10⁶ cpm/µg by the random primer method. The following cDNA probes were used: IGF-I, provided by P. Rotwein, Washington University, St. Louis, MO; IGF-FBP-3, a kind gift from D. Powell, Baylor University, Houston, TX; IGF-1R, kindly provided by Genentech, Inc., San Francisco, CA. Filters were washed for 20 min at 22°C in 2X standard saline citrate (1 x standard saline-citrate is 150 µM NaCl-1.5 mM sodium citrate)-0.1% SDS, followed by 60 min at 65°C in 0.5X standard saline-citrate-0.1% SDS. Autoradiography was performed on Kodak X-omat AR X-ray film with an intensifying screen at -70°C.

RT-PCR Analysis. Reverse transcription of RNA into cDNA was performed by incubating 1 µg of total cellular RNA with 50 µl of 1X reverse transcription buffer (GIBCO BRL)-100 µg/ml bovine serum albumin-0.5 mM deoxyribonucleoside 5'-triphosphates-250 µg/ml oligo(dT)₁₂₋₁₈ (Pharmacia, Piscataway, NJ)-200 units Moloney murine leukemia virus reverse transcriptase (GIBCO BRL) at 37°C for 60 min. PCR was performed at a final concentration of 1X PCR buffer-50 µM deoxyribonucleoside 5'-triphosphates-1 µM each 5' and 3' primers-2.5 units thermostable Taq polymerase (Perkin-Elmer Cetus, Norwalk, CT)-5 µl cDNA template in a total volume of 50 µl. The mixture was overlaid with 75 µl mineral oil and then amplified with a thermal cycler (Perkin-Elmer Cetus). The amplification profile consisted of denaturation at 94°C for 30 s, primer annealing at 55°C for 30 s, and extension at 72°C for 40 s. The number of amplification cycles were as follows: for IGF-I, 35; IGF-1R, 35; IGF-FBP-3, 30; β-actin, 30. Oligonucleotide primers were synthesized on an Eppendorf DNA synthesizer (General Clinical Research Center, New York University Medical Center). The IGF-1A primers were from nucleotides 2399-3926 which include a portion of exon 3, producing a 297-base pair product (56). The IGF-IR primers were from nucleotides 3997-4426, producing a 266-base pair product (57). The IGF-FBP-3 primers were from 8391-8761, producing a 370-base pair product (58). The human β-actin primers were from 3076-3425, producing a 349-base pair product (59). Each PCR product mixture (15 µl) was electrophoresed in 2% agarose gels in Tris borate/EDTA buffer. Molecular weight markers (123-base pair ladder; GIBCO BRL) were run with each gel. Gels were stained with ethidium bromide and photographed under UV light. For Southern blot analysis, gels were blotted onto nylon filters (BA 85; Schleicher & Schuell) electrophoretically with 1X Tris borate/EDTA as the transfer buffer. Blots were baked at 80°C for 2 h to fix the DNA. The specific PCR products were labeled with [32P]dCTP by random priming. Prehybridization/hybridization and washes were performed as described previously (60).

RESULTS

Growth-stimulating Effect of IGF-I. In order to assess the effect of IGF-I on cell proliferation, we performed 3-day culture experiments in serum-free medium or with growth factors (IGF-I, PDGF-AB, or fetal calf serum). The results of these studies displayed as percentages of growth during the 3-day growth period revealed increases in cell growth when serum-free medium was supplemented with fetal calf serum (94 ± 15%, mean ± SEM, P < 0.01), PDGF-AB (104 ± 18%, P < 0.01), or IGF-I (76 ± 26%, P < 0.05) (Fig. 1). In contrast, cells in control medium demonstrated a 24 ± 8% decrement in cell density, probably reflecting cell death during 3 days of growth factor deprivation. The addition of exogenous IGF-I to 2 different human mesothelioma cell lines did not enhance their proliferative response (data not shown).

IGF-I mRNA Expression. Hybridization of an IGF-I cDNA probe which detects both IGF-IA and IGF-IB to human liver polyadenylated RNA demonstrated 3 mRNA species (1.1, 1.3, and 7.6 kilobases) as reported by others (31, 61). In contrast, however, cultured normal mesothelial cells and 3 mesothelioma cell lines expressed IGF-I mRNA as a single 1.3-kilobase mRNA by Northern analysis (Fig. 2). A sarcomatous mesothelioma cell line (lane 4) expressed IGF-I mRNA at levels higher than two epithelial mesothelioma cell lines (lanes 2 and 3) and normal mesothelial cells (lane 1). The relative amounts of RNA loaded into each lane are indicated in Fig. 2, bottom, demonstrating hybridization to the control gene, pH7, a non-cell cycle-regulated gene (62). Detection of IGF-I gene expression required long exposure times of up to 9 days, reflecting the relatively low abundance of this mRNA. We then examined by RT-PCR 5 normal and 11 malignant mesothelial cell lines, including the ones studied by Northern analysis. The PCR product after Southern blotting demonstrated the presence of the expected 297-base pair IGF-I amplification product in all normal mesothelial cell samples (Fig. 3, lanes 1-5: lanes 1 and 2, normal mesothelial cell lines; lanes 3, 4, and 5, normal mesothelial cells from pleural effusions) and mesothelioma.
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Fig. 1. Growth response of normal human mesothelial cells to exogenous IGF-I. Three-day cultures of cells were grown in serum-free media, fetal calf serum (10%), IGF-I (100 ng/ml), or PDGF-AB (10 ng/ml). Cell density was measured at 1.48 pm after napthol blue black staining as described in “Materials and Methods.” The data are expressed as percentages of growth during the 3-day period. Column (bar), mean (±SEM) of triplicate wells. *P < 0.05 compared to medium alone; **P < 0.01 compared to medium alone.

DISCUSSION

IGFs are produced in the liver and exhibit insulin-like and growth-promoting activities. Local activity of IGFs has been detected in many tissues, suggesting that these growth factors are involved in autocrine or paracrine growth regulation (32, 68-70). IGF-I stimulation of tumor cell growth has been reported for breast carcinoma (18, 19), colon carcinoma (20), liposarcoma (20), rat medullary thyroid carcinoma (21), leiomyoma and leiomyosarcoma (22), pancreatic carcinoma (23), lung carcinoma (24-27), ovarian carcinoma (28), fibrosarcoma (29), and osteosarcoma (30). These observations suggest that IGF-I is an important growth factor in tumorigenesis.

In order to test this hypothesis in mesotheliomas, we first defined whether exogenous IGF-I is mitogenic for mesothelial cells. Our cell proliferation studies demonstrated that exogenous IGF-I was indeed

cell lines (lanes 6–16: lanes 7 and 11, sarcomatous mesothelioma cell lines; lanes 6 and 16, biphasic mesothelioma cell lines; lanes 8–10, 12–15, epithelial mesothelioma cell lines). Fig. 3, bottom, demonstrates amplification of the control gene β-actin.

IGF-I Receptor mRNA Expression. The IGF-I receptor is a tyrosine kinase receptor distinct from the insulin receptor despite extensive homology and has a higher binding affinity for IGF-I than IGF-II. IGF-IR mRNA expression was detected by Northern analysis in only one patient sample of normal mesothelial cells and not in mesothelioma cell lines (data not shown). However, the expected amplification product of 266-base pair was detected in all normal and malignant mesothelial cells by using RT-PCR (Fig. 4). The corresponding amplification of β-actin is the same as that in Fig. 3.

IGFBP-3 mRNA Expression. The main carrier of IGFs in the human vascular compartment is a M, 150,000 binding protein complex, including the protein IGFBP-3 and the IGF-I ligand (58, 63). IGFBP-3 may modulate the biological activity of IGF-I both enhancing or inhibiting cellular proliferation depending on culture conditions (49–52). Northern blot analysis of IGFBP-3 mRNA expression of normal and malignant mesothelial cells revealed a single 2.5-kilobase gene transcript (Fig. 5; lane 1, normal; lanes 2–6, malignant mesothelioma). One sarcomatous mesothelioma cell line (lane 5) produced a striking amount of IGFBP-3 mRNA. Interestingly, the same cell line demonstrated increased IGF-I mRNA levels (Fig. 2). Five normal and 11 malignant mesothelial cell samples revealed the expected amplification product in all normal mesothelial cell samples and mesothelioma cell lines when RT-PCR was used (Fig. 6).

IGF-I and IGFBP-3 Protein Expression. Since normal and malignant mesothelial cells express mRNAs for IGF-I, IGF-I receptor, and IGFBP-3, we next examined the conditioned media from cultured normal and malignant mesothelial cells for the presence of IGF-I and IGFBP-3 by specific radioimmunoassay. IGF-I was detected in normal (3 of 5) and malignant (10 of 11) mesothelial cell-conditioned medium (Fig. 7A). Conditioned media from malignant mesothelial cells did not contain more IGF-I (0.136 ± 0.024 ng/ml, mean ± SEM) than that of normal cells (0.120 ± 0.080 ng/ml). Conditioned media from non-small cell lung cancer cell lines (SK-MES-1, A549, and Calu-3) were used for comparison and contained a mean IGF-I protein content (0.233 ± 0.088 ng/ml) comparable to that reported by others (64–66) and was only slightly higher than that for both normal and malignant mesothelial cells. IGFBP-3 was also readily detected in conditioned media from normal (15.9 ± 1.3 ng/ml) and malignant (18.5 ± 3.2 ng/ml) mesothelial cells (Fig. 7B) at levels comparable to that of non-small cell lung cancer cell lines (24.0 ± 7.3 ng/ml) which have been reported to release both IGFBP-1 and -3 proteins into conditioned medium detected by immunoblotting (67).

IGFs are produced in the liver and exhibit insulin-like and growth-promoting activities. Local activity of IGFs has been detected in many tissues, suggesting that these growth factors are involved in autocrine or paracrine growth regulation (32, 68-70). IGF-I stimulation of tumor cell growth has been reported for breast carcinoma (18, 19), colon carcinoma (20), liposarcoma (20), rat medullary thyroid carcinoma (21), leiomyoma and leiomyosarcoma (22), pancreatic carcinoma (23), lung carcinoma (24-27), ovarian carcinoma (28), fibrosarcoma (29), and osteosarcoma (30). These observations suggest that IGF-I is an important growth factor in tumorigenesis.

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IGF gene expression in human pleural mesothelial cells

Fig. 3. Top, IGF-I gene expression in normal and malignant mesothelial cell lines by RT-PCR and Southern blotting. A 297-base pair IGF-I DNA probe was used. Bottom, ethidium bromide-stained 2% agarose gel demonstrating amplification of the control gene β-actin. Lanes 1–5, normal mesothelial cells; lanes 6–16, malignant mesothelioma cell lines (lanes 7 and 11, sarcomatous mesothelioma cell lines; lanes 6 and 16, biphasic mesothelioma cell lines; lanes 8–10, 12–15, epithelial mesothelioma cell lines).

Fig. 4. IGF-IR gene expression in normal and mesothelial tumor cell lines by RT-PCR, followed by Southern blotting. A 266-base pair IGF-I receptor DNA probe was used. The corresponding amplification of the control gene β-actin is the same as that in Fig. 3. Lanes as in Fig. 3.

Although IGF-I is believed to be an autocrine growth factor in various cancers, expression of IGF-I mRNA, in contrast to immunoreactive IGF-I, by malignant epithelial cells has not been frequently described. In this study we have shown that both IGF-I gene transcript and protein were expressed by normal and malignant mesothelial cells. We have also shown that normal and malignant mesothelial cells, like several other cell lines, expressed the IGF-I receptor mRNA. Malignant mesothelioma can now be added to a very limited list of malignancies which have been reported in the literature to express IGF-I receptors. Most of the evidence in the literature has been based on cross-linking, ligand-binding, and receptor blockade...
studies as reviewed by Cullen et al. (71). IGF-IR mRNA expression has been described in only a few malignancies thus far: primitive neuroectodermal tumors (72), breast cancer cell lines and tumors (73), ovarian carcinoma (28). In our studies, not only was the receptor expressed at the mRNA level but the presence of a functional IGF-1 receptor on NHM cells was suggested by our cell proliferation studies. Furthermore, we detected IGFBP-3 gene expression by Northern analysis in cultured normal mesothelial cells and mesothelioma cell lines. By RT-PCR analysis, all normal and mesothelioma cell lines demonstrated expression of the IGFBP-3 mRNA transcript. The peptide was found in significant concentrations in the conditioned media of all normal and mesothelioma cell lines like other cells in culture including human fibroblasts (74) and human umbilical vein endothelial cells (75). The biological significance of IGF-binding proteins produced by NHM and mesothelioma cells is not clear at this time. However, a number of studies have demonstrated that these proteins modulate cellular responses to IGF-I stimulation. The predominant in vitro effect of purified IGFBP-3 is to inhibit the actions of exogenous or endogenous IGF-I. This inhibition is mediated by the effective removal of IGF-I availability to IGF-I receptors by the binding of IGF-I to IGFBP-3 under conditions of coincubation (49, 50). Potentiation of IGF-I action in vitro by IGFBP-3 has also been reported under particular experimental conditions. In contrast to the finding of DeMellow and Baxter (49), Elgin et al. (51) demonstrated under different coincubation conditions that a marked enhancement of DNA synthesis and cell proliferation resulted. Potentiation of IGF-I action is also observed when it is added as a stoichiometric complex, presumably because it allows a continuous slow release of IGF-I similar to an in vitro model in which IGF-I is added intermittently, thereby avoiding down-regulating the IGF-I receptor (52). Release of IGF-I may occur by mass action or upon association with cells. Potentiation of IGF-I-stimulated thymidine incorporation was also noted when cells were preincubated with IGFBP-3 for 8–48 h before adding IGF-I to the system (49). This effect of IGFBP-3 is what we observed when NHM cells were preincubated for 8 h with increasing concentrations of IGFBP-3. The effect was dose dependent with optimal potentiation of IGF-I-stimulated cell proliferation occurring with 100 ng/ml of recombinant IGFBP-3. In contrast, coincubation of IGFBP-3 and IGF-I inhibited IGF-I-stimulated NHM cell proliferation. An explanation for the biological activities of the IGFBPs is suggested from various reports: cell surface-associated IGFBPs can enhance IGF-I action, whereas soluble IGFBPs inhibit IGF-I action (76). Pretreatment with IGFBP-3 may increase the cell surface-associated component, which could then enhance IGF-I action, whereas coincubation of IGFBP-3 and IGF-I would tend to result in preferential sequestering of IGF-I peptide, thus decreasing its bioavailability (49).

For IGF-I to be considered an autocrine growth factor, the peptide must be synthesized by the cell that is affected by its presence, and the cell must possess all the necessary functional components for the autocrine loop, such as the corresponding receptor and the necessary binding protein in the case of IGF-I. Our results suggest that IGF-I exerts its growth-promoting effects on mesothelial cells through an autocrine pathway. The precise mechanisms of IGF-I-stimulated autocrine action in mesothelial cells are not clear. Whether IGF-I interacts with its receptor in the extracellular or intracellular compartment will help delineate the pathway for the autocrine effects of IGF-I. The
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cellular location of the interaction of IGF-I with its receptor is of particular interest since concurrent synthesis of IGF-I and IGF-I receptor protein could permit their intracellular interaction. Recent evidence from studies in a rat thyroid cell line, FRTL-5, suggests that the dominant mechanism of the autocrine action of IGF-I is the secretion of IGF-I and its interaction with surface receptor molecules (77).

This study is the first to identify IGF-I, IGFBP-3, and IGF-IR gene expression by normal and malignant mesothelial cells and to demonstrate a functional mitogenic response to IGF-I in normal human mesothelial cells. These findings suggest that IGF-I may function as an autocrine growth factor in proliferating mesothelial cells which through enhanced cell division may make these cells susceptible to aneuploidy and cell transformation by asbestos fibers.

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REFERENCES


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