Insulin-like Growth Factor 1 (IGF-1) Receptors, IGF-1, and IGF-2 Are Expressed in Primary Human Sarcomas

Ato Sekyi-Otu, Robert S. Bell, Cara Ohashi, Michael Pollak, and Irene L. Andrulis

INTRODUCTION

Bone and soft-tissue sarcomas are relatively rare tumors representing approximately 1% of human cancers. These tumors tend to present in young adults; 75% of patients afflicted with osteosarcoma, for example, are between the ages of 15 and 25 years. Despite current management protocols, about 50% of patients with bone and soft-tissue sarcomas eventually will succumb to their disease (1, 2). The identification of genetic alterations in sarcomas might provide prognostic markers for the disease and may permit novel approaches to therapy that could improve outcome.

There is ample evidence that some human malignancies depend on specific growth factors and receptors for optimum tumor growth. The IGFs mitogenic signal transduction system involves ligands, receptors, and binding proteins that have been shown to be mitogenic for malignant cell lines of both epithelial and mesenchymal origin (3–12). Relationships between IGF ligand, receptor, and oncogenes have been investigated (13–16). The IGF-1 receptor is a transmembrane heterotetramer that mediates the cellular effects of IGF after binding of the ligand to the extracellular domains of the receptor. Expression of IGF receptors overexpression in primary sarcoma specimens. The objectives of the current investigations were, therefore, to evaluate expression of IGF-1 receptor by both competitive binding and RT-PCR techniques, to determine expression of IGF-1 and IGF-2 ligands by RT-PCR in these specimens, and to evaluate gene amplification as a possible mechanism of IGF-1 receptor overexpression in primary sarcoma specimens.

MATERIALS AND METHODS

Preparation of Specimens. Samples from surgically resected tumors were obtained from viable regions of the tumor and immediately flash frozen in liquid nitrogen. Frozen sections from adjacent regions confirmed the presence of viable tumor.

Cells and Cell Cultures. MCF-7 cells were obtained from Dr. R. Buick (Princess Margaret Hospital, Toronto, Ontario, Canada). MDA-468 and T47-D, established breast carcinoma cell lines, were purchased from the American Type Culture Collection (Rockville, MD). NCI H69, a small-cell lung cancer line, and the other cell lines were maintained in vitro in a-MEM (GIBCO) supplemented with 10% PCS at 37°C, whereas RPMI 7666, a lymphoblastic line, was maintained in RPMI 1640 and 20% FCS.

IGF-binding Studies. Binding of recombinant IGF-1 (Amersham) and affinity labeling of IGF-1 receptors were performed on plasma membrane-enriched subcellular fractions of sarcoma specimens prepared by differential centrifugation (12, 31). Human breast carcinoma cell lines MCF-7 and T47-D and human placenta served as positive control tissues. Affinity-labeling studies confirmed that greater than 80% of binding of the radioligand was to a protein of the IGF-1 receptor gene construct and incubation with IGF-1, and transformed NIH 3T3 cells that were implanted into nude mice formed aggressive tumors.

Although previous in vitro investigations have demonstrated expression of IGF-1 receptors (3–12) and IGF-1 and -2 ligands (26–30) in cell lines derived from mesenchymal and epithelial tissues as well as cancers, there has been limited investigation of IGF receptors or ligands in primary sarcoma specimens. The objectives of the current investigations were, therefore, to evaluate expression of IGF-1 receptor by both competitive binding and RT-PCR techniques, to determine expression of IGF-1 and IGF-2 ligands by RT-PCR in these specimens, and to evaluate gene amplification as a possible mechanism of IGF-1 receptor overexpression in primary sarcoma specimens.

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2 To whom requests for reprints should be addressed, at Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 600 University Ave., Toronto, Ontario, Canada M5G 1X5.
3 The abbreviations used are: IGF, insulin-like growth factor; AS, asparagine synthetase; RT-PCR, reverse-transcription PCR.
into guanidinium thiocyanate; RNA was extracted by ultracentrifugation at 4°C, the sample was ethanol precipitated and resuspended in diethyl pyrocarbonate-treated water.

RT-PCR. Oligonucleotides specific to IGF-1 receptor mRNA were designed by Dr. A. Axlerad (University of Toronto, Ontario, Canada) from known genomic and cDNA information (33, 34). Primers for the IGF-1 receptor (produced by K. Deugan, Queens’ University, Kingston, Ontario, Canada) included R1: 5′-ACCCGGAGTACTCGACGCT-3', corresponding to nucleotides 2975–2994 in exon 14; and the antisense primer R2: 5′-CACAGACCTTTGTGGAGAA-3', corresponding to nucleotides 3185–3204 in exon 16. The amplified 226-bp product was specific to the IGF-1 receptor. Expression of the housekeeping gene AS provided an internal control for the amount of RNA template in each RT-PCR aliquot. Specific oligonucleotides were similarly synthesized for AS based upon known sequences (35, 36). The sense sequence A1: 5′-ACATTTAAGCCTCGCGAC-3' corresponds to nucleotides 674–793 in exon 6, whereas IF2: 5′-GCCCACGGGGTATCTGGGGAA-3' from sequence 867-886 in exon 6. The predicted 313-bp product was AS specific.

Similarly, oligo-specific nucleotides for human IGF-2 mRNA were deduced from the known genomic and cDNA sequences (39–41). Sense primer F1: 5′-CTGTGGGACACCCCTCCAGTCTC-3' corresponds to sequence 109–129 in exon 5, whereas IF2: 5′-GCCCACCGGTATCGCGAGAA-3' corresponds to sequence 322–333 in exon 6. AS primers A1 and A3 (above) provided an internal control for IGF-1 RT-PCR.

Two hundred ng of total RNA were reverse transcribed into single-stranded cDNA using a cocktail of 50 mm Tris-HCl (pH 8.3), 75 mm KCl, 3 mm MgCl2, 10 mm DTT, 50 ng/μl of random hexadeoxynucleotide primer (Pharmacia), 8 units/μl RNase inhibitor (Promega), and 25 units/μl of Moloney murine leukemia virus reverse transcriptase (Bethesda Research Laboratories) incubated at 37°C for 1 h. After inactivation at 95°C for 5 min, 100 ng of the cDNA product was added to a PCR cocktail consisting of 2.8 μM primers R3, R4, A1, A3, and 675 pmol deoxyxribonucleotides triphosphate (Pharmacia); 10 mm Tris-HCl, pH 8.3; 50 mm KCl; 1 mm MgCl2; 0.01% gelatin; and 0.08 units/μl of Thermus aquaticus polymerase (Perkin-Elmer). (IGF-1 RT-PCR required 0.8 mm MgCl2.) After a 4-min hot start at 94°C, primers were annealed to template for 1 min; extension was at 72°C for 1 min, and denaturation was at 94°C for 30 s in a Perkin-Elmer Cetus DNA thermocycler for 26 and 28 cycles. PCR products were electrophoresed on a 12% polyacrylamide gel, visualized by ethidium bromide staining, and quantitated by densitometry (Molecular Dynamics, ImageQuant Software, Sunnyvale, CA). Experiments were performed in triplicate.

Quantitation of Levels of Expression of IGF-1 Receptor, IGF-1, and IGF-2 by RT-PCR. The level of IGF-1 receptors in the sarcoma specimens was assayed by both RT-PCR and affinity-binding studies. Expression of IGF-1 receptors and IGF ligands has been demonstrated previously in several established breast cancer cell lines by RNase protection assays, Northern blot analysis, and/or IGF-binding studies (3, 33). These cell lines were used as positive controls for each of the genes of interest.

Before assaying sarcoma specimens, we determined the in vitro kinetics and yield of PCR products as described previously (42) following coamplification of control-cell line cDNA with IGF-1 receptor (or IGF-2 receptor) and AS primers. Preliminary time course experiments were performed using known positive control cell lines for IGF-1 (RPMI 7666 and NCI H69), IGF-2 (NCI H69), and IGF-1 receptor (MCF-7, MDA-468, and T47-D) to determine the optimal number of cycles of PCR to which cDNA products should be coamplified, while still observing predicted exponential production of respective PCR products of interest (IGF-1, IGF-2, or IGF-1 receptor) and the internal control AS (Fig. 1). PCR yields in the controls were plotted on semilogarithmic graphs (data not shown) to determine the appropriate cycle numbers to evaluate relative levels of expression in patient samples. Experiments were carried out from 22 to 28 cycles to ensure a linear range. Because the quantity of amplified AS fragments is assumed to be proportional to the amount of initial mRNA template, a relative level of expression of IGF-1 receptor, IGF-1, and IGF-2 could be determined by normalizing IGF amounts with AS amounts, as determined by densitometry. Finally, relative levels of IGF-1 receptor, IGF-1, and IGF-2 expression in human sarcoma specimens were normalized to the respective levels obtained from cell line controls MCF-7, RPMI 7666, and NCI H69.

Southern Blot Analysis. High-molecular-weight DNA was isolated by standard methods (32). Briefly, DNA (10 μg) was digested with EcoRII, electrophoresed in 0.9% agarose gels, and transferred onto nylon membranes, as described previously (32). Membranes were then UV-crosslinked for 2 min before hybridization with a 730-bp IGF-1 receptor cDNA probe (34) (American Type Culture Collection). Radiolabeled nick-translated probe (Ref. 43; Pharmacia LKD Biotechnology) was hybridized to the blotted membrane in a solution consisting of 50% deionized formamide, 1% SDS, 1 x sodium chloride, 10% dextran sulfate, and 300 μg/ml of salmon sperm DNA at 42°C for 16 h. The filter was initially washed with 2X SSC at room temperature for 10 min, then with 2X SSC and 1% SDS at 50°C for 3 min before being exposed to autoradiographic film at −70°C with an intensifying screen. The radiographic signal was quantified by densitometry as described above.

Nylon membranes were stripped of radiolabeled probe with a solution consisting of 50% deionized formamide, 1% SDS, 1 x sodium chloride, 10% dextran sulfate, and 300 μg/ml of salmon sperm DNA at 42°C for 16 h. The filter was initially washed with 2X SSC at room temperature for 10 min, then with 2X SSC and 1% SDS at 50°C for 3 min before being exposed to autoradiographic film at −70°C with an intensifying screen. The radiographic signal was quantified by densitometry as described above.

RESULTS

Analysis of IGF-1 Receptor Expression in Sarcomas by RT-PCR. Fig. 2 shows a representative polyacrylamide gel of IGF-1 receptor PCR products from patient specimens and control cell lines. Twelve

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of 29 sarcomas evaluated by RT-PCR had IGF-1 receptor levels comparable to or higher than that of MCF-7, as summarized in Table 1.

IGF-1 Receptor Expression Determined by Affinity-Binding Studies. In addition to use of the molecular RT-PCR technique described above to determine relative IGF-1 receptor expression in patient samples, we used competitive binding of $^{125}$I-labeled IGF-1 as a biochemical assay of IGF-1 receptor. Preliminary studies with known positive control breast cancer cell lines (T47-D, MCF-7, and MDA-468) as well as human placenta provided semiquantitative comparison of the percentage of affinity binding in patient samples. Thirteen of 29 sarcomas showed levels of IGF-1 receptor binding greater than that of MCF-7, as summarized in Table 1. In 24 specimens, both affinity-binding and PCR assays were performed. There was significant concordance between these methods of measuring IGF-1 receptor ($\rho$ coefficient = 0.51, $P = 0.017$, Spearman’s rank coefficient).

Analysis of IGF-1 Receptor Gene Amplification in Sarcomas. To determine whether amplification of the IGF-1 receptor gene was a mechanism by which sarcomas might express high levels of IGF-1 receptors, we performed Southern blot analysis on a subset of the specimens that showed high levels of expression. Densitometry was used to compare autoradiographic intensities of IGF-1 receptor and control neu/c-erbB2 signals. The results indicated that the gene for IGF-1 receptor was not amplified in these tumors.

Table 1 Relative levels of IGF-1 receptors, IGF-1, and IGF-2 in human sarcomas

<table>
<thead>
<tr>
<th>Tumor no.</th>
<th>Sarcoma</th>
<th>% Specific binding of IGF-1 receptor to $^{125}$I-IGF-1</th>
<th>RT-PCR</th>
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<td></td>
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<td>IGF-1</td>
</tr>
<tr>
<td>1</td>
<td>Osteosarcoma 1</td>
<td>1.4</td>
<td>1.5</td>
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<td>Osteosarcoma 2</td>
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<tr>
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<td>Osteosarcoma 3</td>
<td>3.8</td>
<td>1.1</td>
</tr>
<tr>
<td>4</td>
<td>Osteosarcoma 4</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
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<td>Osteosarcoma 5</td>
<td>2.7</td>
<td>4.3</td>
</tr>
<tr>
<td>6</td>
<td>Osteosarcoma 6</td>
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</tr>
<tr>
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<td>Osteosarcoma 7</td>
<td>ND</td>
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<td>Osteosarcoma 9</td>
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<tr>
<td>11</td>
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<td>1.1</td>
</tr>
<tr>
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<td>MFH 2</td>
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<tr>
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<td>Liposarcoma 5</td>
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<tr>
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<td>T47-D</td>
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</tr>
<tr>
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<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>RPMI 7666</td>
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<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>NCI H69</td>
<td>ND</td>
<td>0.00</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* ND, not determined; MFH, malignant fibrous histiocytoma; GCT, giant cell tumor.
Expression of IGF-1 and IGF-2 mRNA. To evaluate expression of IGF-1 and IGF-2, RT-PCR was performed on extracted mRNA aliquots. Figs. 3 and 4 illustrate representative polyacrylamide gels of respective IGF-1 and IGF-2 PCR products from patient specimens and cell lines. Whereas NCI H69 expressed both IGF-1 and IGF-2, expression of IGF-1 was not detectable within the exponential range of PCR product amplification necessary for quantitative densitometry. RPMI 7666 expressed higher levels of IGF-1 and was, therefore, used for quantitative analysis. Twenty-two of 28 specimens expressed IGF-1 levels comparable to or greater than that of RPMI 7666, whereas 17 of 27 tumor samples demonstrated elevated levels of IGF-2 expression (greater than or equal to that of NCI H69). Analysis of IGF-1 (relative to RPMI 7666) and IGF-2 (relative to NCI H69) expression in the sarcoma specimens is summarized in Table 1.

DISCUSSION

Expression of growth factors and/or their receptors may be a significant mechanism by which some sarcomas develop abnormal growth. In particular, in vitro studies using established cell lines in culture have suggested recently that tumors that express IGF-1 receptors may be responding, not only to circulating serum levels of IGF-1 produced by the liver, but also to IGF-1 that is produced by the tumor itself in an autocrine or paracrine manner (10, 45, 46). In addition, in vitro studies have shown clearly that IGF-2, by binding to the IGF-1 receptor, can produce proliferative actions on both normal mesenchymal cells and sarcoma cell lines in culture (18, 46, 47).

In this study, we determined the levels of receptor and ligand evident in sarcoma specimens. All 29 mesenchymal tumors examined in this study demonstrated some identifiable IGF-1 receptor level, as determined by independent RT-PCR and affinity-binding assays. The ubiquitous expression of the IGF-1 receptor in these tumors alone is not surprising because the normal tissues from which these tumors are derived also express the receptor (17, 18). However, 13 of 25 (by affinity-binding studies) and 12 of 29 (by RT-PCR) of these samples expressed levels of IGF-1 receptor that are equal to or greater than levels exhibited by MCF-7, a positive control cell line (Table 1) previously shown to be responsive to physiological doses of IGF-1 both in vitro and in vivo (3, 34, 48). The levels of IGF-1 receptors in these 13 human primary tumors also were comparable to or greater than those found in the MGH-OGS osteosarcoma (31) and RIF-1 fibrosarcoma (49) murine models; both of these tumors have been shown to respond to in vivo manipulation of IGF-1 levels in host mice. In contrast, a number of tumors expressed relatively low levels of IGF-1 receptor, similar to the murine SCC-7 squamous cell carcinoma, which does not respond to IGF-1 in vivo.4

Although about 50% of the sarcomas had elevated levels of IGF-1 receptor mRNA, this was not due to DNA amplification of the IGF-1 receptor gene. In a study of breast tumors, only 2% of specimens demonstrated evidence of an increased copy number of the IGF-1 receptor gene (7). Amplification of the IGF-1 receptor gene in sarcomas has not been reported, but the comparatively small subset of tumors examined for gene amplification in our series certainly does not exclude the possibility of IGF-1 receptor amplification in sarcomas.

In this study, IGF-1 receptor expression was evaluated by two independent assays, RT-PCR and the competitive binding assay of receptor affinity. Positive controls common to both assays were used to quantify the levels of receptor expression. Although there was concordance between the techniques, it was only moderate, i.e., tumors that were determined to be high expressers by RT-PCR were not necessarily always high expressers by affinity-binding studies, and vice versa.

There are several potential factors that might cause discrepancy between the values determined by the two assays. Two different species of IGF-1 receptor mRNA are recognized as the products of alternative splicing (33, 50); the efficiency of translation of these species might differ. Untranslated mRNA would not be available for the affinity-binding assay. In addition, IGF-1 receptors with different affinity binding are known to exist (51, 52). Furthermore, hybrids of the insulin receptors and IGF-1 receptor may exist in certain tumor cell lines (51). The functional significance of these receptors is not yet known; however, such receptors would have altered affinity for IGF-1 and insulin ligands. Finally, preferential down-regulation of receptor numbers on the cell membrane by ligand may have occurred. Several ligands, including insulin, IGF-1, and low-density lipoprotein, have been shown to be internalized into the cell with their respective receptors, where the ligand-receptor complex is degraded (51, 53). Thus, tumors that overexpressed the IGF-1 receptor transcripts may have down-regulated receptor numbers upon binding of the IGF-1 or IGF-2 ligand. Although there are a variety of factors that would tend to cause nonconcordance between the assays, significant correlation was found to exist.

The evaluation of IGF-1 and IGF-2 ligand expression suggests that some bone and soft-tissue sarcomas are capable of IGF-1 receptor-mediated proliferation by a mechanism of autocrine and/or paracrine

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4 A. Sekyi-Otu, unpublished observations.
strategies could be applied as possible therapy for controlling tumor growth on anabolic androgens for prostate cancer. Similarly, endocrine manipulation of dependence on estrogens for breast cancer and dependulation of serum IGF might be feasible in IGF-responsive human sarcomas. The RPMI 7666 cell line expressed levels of IGF-1 receptor greater than the MCF-7 cell line and those detected in the higher expressing RPMI 7666 cell line might be physiologically significant. In our panel of human sarcomas, 23 of 28 specimens demonstrated levels of IGF-1 greater than or equal to RPMI 7666 levels (Table 1).

Similarly, exogenous IGF-2 has been shown to produce a mitogenic effect on MCF-7 cells in vitro (34), mediated through the IGF-1 receptor, although much higher levels of IGF-2 peptide are required to produce effects equivalent to those of IGF-1. It is likely that levels of IGF-2 that were comparable to or higher than those observed in NCI H69 might be physiologically significant in vivo. Seventeen of 27 sarcomas exhibited this level of expression of IGF-2 mRNA.

More accurate determination of the bioavailability or bioactivity of specific levels of IGF-1 or IGF-2 ligand identified in sarcomas will require evaluation of expression of IGF-binding protein levels in sarcomas; the effect of any one of six characterized IGF-binding proteins may be inhibitory and/or stimulatory, as well as tissue specific (55, 56). Other factors that will likely require evaluation in patients harboring potentially IGF-responsive sarcomas include serum levels of IGF-1, IGF-2, and binding proteins.

To date, few studies have attempted either to investigate the expression of IGF receptors and IGF ligands in specimens obtained at surgery or to determine any clinical implications of IGF dependency in vivo. We have recently demonstrated evidence of IGF dependence in murine MGH-OGS (31) and RIF-1 murine sarcomas (49), which expressed levels of IGF-1 receptor greater than the MCF-7 cell line. The in vivo local growth and metastasis of these murine tumors could be altered by changing serum levels of IGF. These murine experiments suggested that novel therapeutic approaches based on manipulation of serum IGF might be feasible in IGF-responsive human tumors.

This analysis of human sarcomas suggests that approximately 50% of these human tumors might be responsive to IGF-1 in vivo. More specifically, we suggest that the 13 tumors expressing IGF-1 receptor at levels equal to or greater than those of MCF-7 might respond to pharmacological manipulation of patient IGF-1-mediated proliferation. Presently, accepted endocrine therapies for cancer include the exploitation of dependence on estrogens for breast cancer and dependence on anabolic androgens for prostate cancer. Similarly, endocrine strategies could be applied as possible therapy for controlling tumor progression in patients whose sarcomas are determined to be IGF dependent.

Expression of IGF-1 receptors and IGF-1 and IGF-2 ligands was demonstrated in a wide variety of human sarcoma specimens, suggesting the presence of autocrine and/or paracrine regulatory pathways in addition to endocrine pathways that are available for aberrant tumor growth and progression. In addition to this effect on cell proliferation, IGF ligands have been demonstrated to act as motility factors for several cell lines in vitro (10, 57). It is, therefore, plausible that overexpression of IGF-1 or IGF-2 ligands in human tumors might predispose certain tumors to metastasis in addition to stimulating proliferation. Further investigations into the role of IGF in sarcomas (as well as other cancers) may lead to improved stratification of outcome and novel therapeutic modalities based on modifying the response to IGF.

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