Interleukin 6 Acts as a Paracrine Growth Factor in Human Mammary Carcinoma Cell Lines

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ABSTRACT

The effect of interleukin 6 (IL-6) on normal and human mammary carcinoma epithelial cells was studied. IL-6 inhibited the growth of estrogen receptor-positive [ER(+)I breast cancer cell lines, which underwent apoptosis with prolonged treatment. In contrast, ER(-) breast cancer cell lines were resistant to IL-6-mediated growth inhibition. By examining the components of the IL-6 receptor (IL-6R) system, we found that ER(+I breast cancer cells expressed predominantly soluble IL-6Ro, whereas the ER(-) breast cancer cells expressed primarily the transmembrane form of the IL-6R, gpl30. In addition, detectable levels of IL-6 were secreted into the medium by ER(-) but not ER(+) breast cancer cells. Furthermore, the supernatant obtained from IL-6-secreting, ER(-) cells suppressed the growth of IL-6-sensitive, ER(+) breast cancer cells. Although IL-6 is secreted by ER(-) breast cancer cells, this cytokine does not seem to stimulate the proliferation of these cells in an autocrine fashion. These studies indicate that IL-6 can regulate the growth of normal and transformed human mammary epithelial cells differentially, and that IL-6 secretion by some ER(-) breast cancer cells can function as a paracrine growth factor, suppressing the growth of ER(+) breast cancer cells in vitro.

INTRODUCTION

IL-6 is a pleiotropic cytokine involved in the early host response to infection and injury (1). IL-6 acts physiologically to stimulate acute-phase protein synthesis by hepatocytes (2), secretion of adrenocorticotropic hormone by the anterior pituitary gland (3), and immunoglobulin production by activated B cells (4). IL-6 has been shown to enhance, inhibit, or have no effect on the proliferation of various epithelial and hybridoma cells (5), plasmacytoma, and hybridoma cells (6). IL-6 is also involved in the regulation of bone metabolism (7). In culture, IL-6 enhances, inhibits, or has no effect on the proliferation of epithelial cells, depending on the cell type examined. IL-6 also has been shown to inhibit the proliferation of various human breast carcinoma cell lines (T47D, SK-BR-3, MCF-7, and ZR-75-1; Refs. 10-12). In contrast, immortalized MCF-10A cells or MCF-10A int-2-transformed cells are growth stimulated by exogenous IL-6 (13). The mechanisms by which IL-6 inhibits the proliferation of some epithelial cells and stimulates that of others are unclear.

The ability of IL-6 to elicit effects from a cell is dependent on the display of its cognate receptor by the target cell. Two transmembrane glycoproteins are currently known to participate in the IL-6R system (14). IL-6R is a Mr 80,000 protein that binds directly to IL-6 with low affinity (15). The intracellular region of IL-6Rα is short and is not essential for IL-6 signaling. The IL-6 signal is transduced through the transmembrane protein, gpl30, which is involved in the formation of high-affinity IL-6-binding sites through its association with IL-6Rα (16). sIL-6Rα has been shown to bind to IL-6 in solution and to augment the activity of IL-6 as a result of the binding of the IL-6-sIL-6Rα complex to membrane-bound gpl30 (17).

Previous studies on subclones of T47D human breast cancer cells with differential sensitivity to IL-6-mediated cytotoxicity indicated that the differences could not be accounted for by qualitative or quantitative differences in IL-6Rs (18). To define the mechanism of IL-6-mediated cytotoxicity on human mammary epithelial cells better, we have examined the effects of this cytokine in vitro on a series of cells, including NMECs derived from reduction mammoplasties, as well as three ER(+) breast cancer cell lines (MCF-7, T47D, and ZR-75-1) and three ER(-I breast cancer cell lines (MCF-7, T47D, and ZR-75-1) and three ER(-) breast cancer cell lines (MCF-7, T47D, and ZR-75-1). Our results indicate that IL-6 inhibits the proliferation of normal breast epithelial cells as well as three ER(+) breast cancer cell lines. However, despite the presence of IL-6Rα and gpl30, the ER(-) breast cancer cell lines were not inhibited by IL-6. In addition, these studies indicate that ER(-) breast cancer cells can secrete IL-6 and can inhibit the growth of IL-6-sensitive, ER(+) breast cancer cells.

MATERIALS AND METHODS

Cells and Cell Cultures. Human NMECs were derived from reduction mammoplasties (Clonetics Corp., Palo Alto, CA). ADRMCF-7 cells are a multidrug-resistant variant of MCF-7 breast cancer cells selected for resistance to the antineoplastic agent adriamycin. NMECs were cultured in mammary epithelial basal medium (Clonetics Corp., Palo Alto, CA). MCF-7 breast cancer cells selected for resistance to the antineoplastic agent adriamycin. NMECs were cultured in mammary epithelial basal medium (Clonetics Corp., Palo Alto, CA). ADRMCF-7 cells are a multidrug-resistant variant of MCF-7 breast cancer cells selected for resistance to the antineoplastic agent adriamycin. NMECs were cultured in mammary epithelial basal medium (Clonetics Corp., Palo Alto, CA).
proved MEM from GIBCO-BRL (Gaithersburg, MD) supplemented with 10% FCS. The U266 cell line was cultured in RPMI 1640 supplemented with 10% FBS. All cell cultures were maintained at 37°C in a humidified atmosphere of 5% CO₂.

Reagents. rhIL-6 produced from human T lymphocytes was purchased from Boehringer-Mannheim (Indianapolis, IN). The specific activity of the cytokine was assayed in B-cell hybridoma 7TD1 cells and was found to be 1 x 10⁸ units/mg. Polyclonal goat antihuman IL-6-neutralizing antibody was purchased from R&D Systems (Minneapolis, MN). Antihuman IL-6Ra monoclonal antibodies PM1 and MT18 were described previously (19) and were provided generously by R. P. Nordan (Food and Drug Administration, Bethesda, MD). PM1 recognizes the IL-6-binding domain of IL-6Ra; whereas MT18 does not. The antihuman gp130 monoclonal antibody AM64 was provided generously by T. Kishimoto and K. Yasukawa (Osaka University, Japan).

Cell Proliferation Assay. Cells were seeded at 5 x 10⁵ cells/well in a 96-well microtiter plate. The cells were fed with fresh medium containing serial 1:5 dilutions of rhIL-6 after 2 days. After 48 h, cells were incubated with [³H]thymidine (10 μCi/ml, 10 μl) for 2 h at 37°C. The cells were washed twice with ice-cold PBS, treated with 5% trichloroacetic acid for 30 min at 4°C, and washed three times with 5% trichloroacetic acid. The precipitate was dissolved in 0.1 ml 0.2 N NaOH at 37°C for 1 h and neutralized by 0.1 ml 0.2 N HCl. Cell-associated radioactivity was measured using a liquid scintillation counter. All experiments were repeated twice with either triplicate or quadruplicate determinations and compared with control cultures incubated without rhIL-6. Neutralization and receptor blockade experiments were done in either 12- or 24-well plates following the same procedure.

DNA Laddering Assay. Cells were seeded at 500 cells/ml in a 25-cm² flask. On day 2, fresh medium containing 5 ng/ml rhIL-6 was added. After 6 days of IL-6 exposure, all cells (floating and adherent) were harvested with trypsin and washed twice with ice-cold PBS. The cells were incubated at 4°C for 2 h in lysis buffer [20 mM Tris (pH 7.4), 5 mM EDTA (pH 8.0), and 0.05% Triton X-100]. High-molecular weight DNA was spun down, and the supernatant was treated with RNase A for 1 h at 55°C, followed by Sds and proteinase K treatment for 1 h at 55°C. Following phenol and chloroform extraction, DNA fragments were precipitated with glycogen in isopropanol and analyzed on a 1.5% agarose gel.

Flow Cytometry. Cells were detached with ice-cold PBS without calcium and magnesium and 5 mM EDTA. Cell suspensions were prepared in HBSS (without phenol red) containing 1% BSA and 0.1% sodium azide. Cells (10⁶/30 μl buffer) were incubated on ice for 30 min with 10 μl appropriate antibodies or biotinylated IL-6 and washed twice before analysis. Analysis was performed using a FACScan (Becton Dickinson, Mountain View, CA) flow cytometer with Lysis II software; cells were gated according to size and propidium iodide staining.

RT-PCR. Total RNA was isolated by the rapid isolation method described by Maniatis et al. (20). Human mammary gland total RNA from nonlactating females was obtained from Clontech Laboratory, Inc. (Palo Alto, CA). The first-strand cDNA was synthesized by random hexamer with less than 1 μg total RNA in a 20-μl reaction with or without reverse transcriptase according to the manufacturer’s recommendation (Perkin-Elmer, Norwalk, CT). The cDNA product was divided into equal aliquots, adjusted for salt and deoxynucleotide triphosphate concentrations, and subjected to 30 cycles of amplification with appropriate primers. Cycling conditions were denaturation at 94°C for 45 s, annealing at 60°C for 45 s, and extension at 72°C for 1 min. All procedures were performed simultaneously on all cell lines to normalize reaction conditions. IL-6 primers were purchased from Clontech. The gp130 primers were 5'-GCA AGA TGT TGA CGT TGC AGA CCT G-3' (nucleotides 251-276) and 5'-GGG CAT TCT CTG CCT CTA CCC AGA C-3' (nucleotides 866-841). The PCR products were separated on a 1.5% agarose gel and transferred to HyBond-N membrane. Southern blot analysis was performed with antisense oligo probes according to the manufacturer’s recommendations (Stratagene, La Jolla, CA).

hIL-6 and sIL-6R ELISA. Breast cancer cells (4 x 10⁴ cells/25-cm² flask in 5 ml media) were cultured in 5% FBS for 5 days. The supernatants were harvested each day, centrifuged (100 X g) to remove any particulate material, and stored at 4°C. The ELISA was performed using a hIL-6 and sIL-6R Quantikine kit from R&D Systems following the manufacturer’s instructions.

RESULTS

Effect of rhIL-6 on Breast Epithelial Cells. The effect of rhIL-6 on the growth of normal and transformed breast epithelial cells is shown in Fig. 1, A–C. Human NMECs displayed a dose-dependent inhibition of [³H]thymidine incorporation following 48 h exposure to rhIL-6 (Fig. 1A). This decrease in [³H]thymidine incorporation following IL-6 treatment was accompanied by a slight decrease in cell number. However, neither gross morphological changes nor changes in cell viability (trypan blue exclusion) were noted.

Three ER(+) breast cancer cell lines also demonstrated an IL-6 dose-dependent inhibition of [³H]thymidine incorporation (Fig. 1B). The growth-inhibitory effects of IL-6 on these cell lines were eliminated by incubation in the presence of anti-IL-6 neutralizing antibodies (data not shown). In contrast, three ER(-) breast cancer cell lines were resistant to IL-6-mediated growth inhibition, as shown in Fig. 1C. IL-6 treatment of AD-RrMCF-7, MDA-MB-231, and HS578T breast cancer cells resulted in little if any growth inhibition by [³H]thymidine incorporation even at the highest IL-6 dose (10 ng/ml).

IL-6 Induces Apoptosis in Breast Carcinoma Cell Lines. Previous studies have shown that IL-6 induces distinct morphological changes, including altered shape and increased motility, in some the ER(+) breast carcinoma cells (21). In the present study, we also noted morphological changes in each of the ER(+) breast cell lines that were inhibited by IL-6 (data not shown). To investigate whether the mechanism of IL-6-mediated cytotoxicity on ER(+) breast cancer cells involved programmed cell death (apoptosis), we examined whether IL-6 induced DNA fragmentation in these cell lines. As shown in Fig. 2, IL-6 treatment of MCF-7 and ZR-75-1 cells was associated with DNA laddering characteristic of apoptosis. In contrast, although NMECs were growth inhibited by IL-6, this cytokine did not induce DNA fragmentation in these cells. Furthermore,
IL-6 treatment of ER(−) breast cancer cell lines Hs578T and MDA-231 did not affect their growth (Fig. 1C), and there was no evidence of DNA fragmentation (Fig. 2).

**IL-6R System in Breast Carcinoma Cells.** To determine whether IL-6-mediated growth inhibition of human mammary epithelial cells is related to the cytokine receptor status, we analyzed the components of the IL-6R system in these breast cancer cell lines. Using FACS analysis, both MCF-7 and ZR-75-1 ER(+) cell lines stained weakly for the surface IL-6Ra. Two ER(−) cell lines (MDA-321 and HS578T), the growth of which was unaffected by the exogenous addition of IL-6, actually showed somewhat higher levels of expression of this molecule on the surface (Fig. 3). Similar results were obtained by FACS analysis using either monoclonal antibody MT18 or biotinylated IL-6. In contrast, we detected a significantly higher amount of the soluble form of IL-6Ra secreted in ER(+) breast cancer cells compared with ER(−) cells (Table 1).

The transmembrane protein gp130, the signal transducer for IL-6, is also required for high-affinity binding of IL-6 to its receptor. Using RT-PCR techniques, gp130 RNA was detected in all breast cancer cell lines, in normal mammary epithelial cell cultures, and in RNA extracted from normal mammary tissue (see below). We also confirmed the presence of gp130 protein in these cell lines by flow cytometry using the monoclonal anti-human gp130 antibody AM64 (data not shown).

We have confirmed the lack of effect of IL-6 on ER binding of estradiol in MCF-7 cells by Scatchard analysis. Using the highest dose of IL-6 (10 ng/ml), which caused maximum cell growth inhibition noted at day 2 (Fig. 1B), we found that there was no change in the ER K_d between control and IL-6-treated MCF-7 cells (control K_d, 0.49 nM; IL-6 K_d, 0.48 nM; data not shown).

**IL-6 Secretion in ER(−) Breast Cancer Cells.** Under physiological conditions, epithelial cells do not secrete detectable levels of IL-6. Because aberrant production of IL-6 has been reported in several solid tumors (22-24), we examined the expression of IL-6 in each of the cell lines by RT-PCR (Fig. 4). IL-6 RNA was undetectable in the three ER(+) breast cancer cell lines. In contrast, each of the three ER(−) breast cancer cell lines displayed high levels of IL-6 RNA. In addition, IL-6 RNA was readily detectable in RNA isolated directly from the mammary gland, which consists of epithelial cells and stromal fibroblasts (Fig. 4). Very low levels of IL-6 RNA were also detected by RT-PCR in normal human mammary epithelial cells.

To determine whether IL-6 RNA detected in human breast cancer cell lines was associated with the secretion of IL-6 protein, the medium from each cell line was assayed for IL-6 protein using an ELISA. Table 2 shows that ADRrMCF-7 and MDA-MB-231 cells secreted IL-6 constitutively over the course of 5 days in culture; IL-6 secretion in HS578T cells was somewhat less. MCF-7 cells, in which no detectable IL-6 RNA was found, did not secrete measurable amounts of the cytokine.

To determine whether the secreted IL-6 protein was biologically active, the supernatant from MDA-MB-231 cells was assayed for its ability to suppress the proliferation of the IL-6-sensitive, ER(+) breast cancer cells. Indeed, as shown in Fig. 5, ZR-75-1 cell proliferation was inhibited by the addition of conditioned medium from MDA-231 cells. Furthermore, this inhibitory effect was at least in part reversed by the addition of...
neutralizing anti-IL-6 antibody to the conditioned medium (Fig. 5). The antibody was also able to neutralize the inhibitory effect of purified IL-6 on ZR-75-1 cells. Moreover, the addition of anti-IL6 antibody in the absence of IL-6 had no effect on these cells. Although we cannot exclude the presence of other inhibitory factors in the MDA-MB-231 supernatant, these studies implicate IL-6 as an MDA-MB-231-derived factor capable of inhibiting IL-6 sensitive, ER(+) human breast carcinoma cells strongly.

In addition to its role as a paracrine inhibitor of normal breast epithelium and some breast cancer cells, IL-6 could function as an autocrine growth factor in breast cancer cells producing IL-6. To examine the possible stimulatory effect of IL-6 on the growth of the three ER(−) cell lines (ADRrMCF-7, HS578T, and MDA-MB-231 cells), which synthesized IL-6, these cell lines were incubated in the presence or absence of either polyclonal neutralizing antibodies to IL-6 or the monoclonal anti-IL-6Ro antibody PM1. None of the cell lines examined displayed significant changes in the rate of proliferation when incubated in the presence of either antibody (data not shown). This finding, coupled with the observation that the exogenous addition of rhIL-6 failed to enhance the proliferation

Fig. 2 Cell growth inhibition by rhIL-6 induces apoptosis in breast carcinoma cell lines. Cells (2500) were seeded in a 25-cm² culture flask. After 1 day to allow attachment, the cells were cultured in medium with or without 5 ng/ml rhIL-6 for 6 days. The experimental procedure for the DNA laddering assay is described in "Materials and Methods."

Fig. 3 Flow cytometric analysis of ER(+) and ER(−) breast cancer epithelial cells using the PM1 or MT-18 antibody, as described in "Materials and Methods." U266 cells were used as positive control cells. The fluorescence of cells stained with the IL-6R PM1 antibody is shown as rightward shift in comparison to the fluorescence obtained with the control antibody MT-18.
of these cells, suggests that IL-6 does not function as an autocrine growth factor in these breast cancer cells in vitro.

DISCUSSION

IL-6 is a multifunctional cytokine with biological activities on a wide variety of cells and a potential regulator of the growth of breast epithelial cells (1–6). Previous studies have shown that IL-6 is present in the conditioned medium obtained from breast stromal fibroblast cultures, raising the possibility that breast epithelial cells can be regulated in a paracrine fashion by IL-6 secreted by stromal fibroblasts (25). Hutchins and Steel have suggested that IL-6 is involved in intercellular signaling between mesenchyme and breast cancer epithelium (26). Conditioned medium generated from human fibroblasts up-regulated the expression of ICAM-1 in breast cancer cells (26). The studies in this report, as well as those of others (11, 13, 25), have shown that IL-6 can regulate the growth of both NMECs and breast cancer cells. In agreement with previous reports, we have confirmed the cell growth-inhibitory effects of IL-6 on three ER(+) breast cancer cell lines (MCF-7, ZR-75-1, and T47D). In addition, we found that the morphological changes and growth inhibition induced by IL-6 in these breast cancer cell lines were associated with apoptosis. Furthermore, although IL-6 inhibited the growth of NMECs, it did not induce apoptosis in these normal breast epithelial cells. This differential response of breast cancer cells and normal breast epithelial cells to IL-6 could represent important differences in cell cycle regulation and in the regulation of apoptosis on normal versus transformed mammary epithelial cells. The escape of normal mammary epithelial cells from negative growth control may represent an important mechanism underlying neoplastic transformation. Although shedding of the soluble form of the IL-6R from ER(+) breast cancer cells is not apparently the mechanism by which the cells protect themselves from the growth-inhibitory effects of IL-6, this phenomenon still may have some functional significance in vivo.

We also have identified differences between ER(−) breast cancer cell lines, which are refractory to IL-6-mediated growth inhibition, and ER(+) breast cancer cell lines, which are sensitive to this cytokine. Indeed, despite their insensitivity to IL-6, the ER(−) breast cancer cell lines expressed both the binding and signal-transducing subunits of the IL-6R complex. We also determined the expression of IL-6 and gp130 in human mammary epithelial cells. Total RNA was reverse transcribed by random primers. The cDNA products were divided into equal aliquots, and PCR amplification was performed with appropriate primers. To normalize the reaction, cDNA products were divided into equal aliquots, and PCR amplification was performed simultaneously for all of the cell lines. The PCR products were verified by size and by Southern hybridization with antisense oligo probes. Similar results were obtained in three experiments using two different preparations of RNA.}

![Fig. 4](https://example.com/fig4.png) **Table 1** Secretion of sIL-6Rα in the medium of breast cancer cell lines

<table>
<thead>
<tr>
<th>Cell lines</th>
<th>sIL-6 Rα (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T47 D</td>
<td>34.58 ± 7.8</td>
</tr>
<tr>
<td>Z R-75-1</td>
<td>42.70 ± 22.2</td>
</tr>
<tr>
<td>MCF-7</td>
<td>74.08 ± 18.4</td>
</tr>
<tr>
<td>ADR/MCF-7</td>
<td>8.22 ± 3.5</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>HS578T</td>
<td>16.65 ± 0.5</td>
</tr>
</tbody>
</table>

*a Results were determined by ELISA. Supernatants were harvested from 5-day cell cultures of each cell line plated at 2 × 10^5 cells/ml in a 25-cm^2 flask. The results represent the mean ± SD of three separate determinations.

**Table 2** IL-6 secretion in the medium of breast cancer cell lines

<table>
<thead>
<tr>
<th>Cell lines</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture medium</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>MCF-7</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>ADR/MCF-7</td>
<td>212</td>
<td>292</td>
<td>468</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>172</td>
<td>448</td>
<td>479</td>
</tr>
<tr>
<td>HS578T</td>
<td>25</td>
<td>40</td>
<td>62</td>
</tr>
</tbody>
</table>

*a Results were determined by ELISA. Supernatants were harvested from each cell line plated at 10^6 cells/ml. The results are expressed as the mean of three determinations from one representative experiment.

![Fig. 5](https://example.com/fig5.png)
have found that the soluble IL-6Ra in these cells can bind IL-6 by staining with biotinylated IL-6 in the FACS analysis (data not shown). Furthermore, we found that the transmembrane form of the receptor, gp130, is present in all of the breast cancer cell lines regardless of their response to IL-6. Thus, the presence of gp130 suggests a mechanism further downstream in the IL-6 signal transduction pathway.

Studies in this report also demonstrated that ER(−) breast cancer cell lines can secrete IL-6 actively in a biologically active form, and that this could suppress the proliferation of ER(+) IL-6-sensitive breast cancer cells in vitro in a paracrine fashion. The secreted cytokine had little or no effect on the proliferation of IL-6-secreting breast cancer cells in vitro. This is in contrast to the growth-stimulatory effect of IL-6 on renal cell carcinoma, multiple myeloma, and Kaposi’s sarcoma in which the sIL6Ra-IL6 autocrine loop has been implicated in the oncogenic process (27-29). Similar to acute myeloid leukemic cells (30), coexpression of IL-6 and its receptor does not have any apparent effects on the growth of ADRrMCF-7, HS578T, and MDA-MB-231 cells.

The role of IL-6 as a paracrine and/or autocrine growth regulator within a heterogeneous population of ER(+) and ER(−) breast cancer cells is not known. Our findings suggest a paracrine effect of ER(−) on ER(+) breast cancer cells via IL-6. Furthermore, previous immunohistochemical studies have indicated that ductal cell carcinomas localized within the breast showed weak IL-6 immunoreactivity, whereas lymph node metastases showed strong IL-6 immunoreactivity (31-33). These findings support the hypothesis that metastatic breast carcinoma cells may become resistant to IL-6 growth inhibition and may secrete IL-6 to gain a selective growth advantage in the metastatic sites (32, 33).

The studies in this report suggest important differences in the IL-6 signal transduction pathway in ER(+) versus ER(−) breast cancer cells, and that these differences lie downstream of the IL-6R and its transmembrane signal transduction protein, gp130.

gp130 is the signal transducer for several cytokines, including IL-6, IL-11, OSM, leukemia inhibitory factor, and ciliary neurotrophic factor. Of these, IL-6 and OSM are known to inhibit breast carcinoma cell growth (34). Because both cytokines rely on gp130 to relay their signals, comparing the effect of OSM and IL-6 on different breast cancer cells may yield important insights into the biochemical cascade triggered by these cytokines. A differential effect of various cytokines was observed previously during myeloid differentiation of M1 leukemia cell lines. Thus, the responsiveness of M1 cells to leukemia inhibitory factor and OSM but not IL-6 can be altered by constitutive expression of the transcription factor stem-cell leukemia in these cells (35). Although stem-cell leukemia has been considered a lineage-restricted transcription factor in hematopoietic cells, the expression of this factor in breast tumors has not been examined. Recent studies from our laboratory (36) and others have shown that the expression of c-myc, another putative, lineage-specific, hematopoietic transcription factor, is detected in breast cancers, and its expression was correlated with estrogen and progesterone receptor expression in these tumor cell lines (37). Thus, the role of hematopoietic differentiation factors in the biology of nonhematopoietic tumors deserves additional study.

The potential role of the ER in the response to IL-6 may have particular importance in the biology of breast cancer in patients. These results generate a number of questions that remain to be considered, including the role, if any, of ER activation relative to IL-6R activation. Furthermore, the level at which the regulation of these two distinct signal transduction pathways is likely to occur may have implications in the biology of breast cancer conversion from an estrogen-responsive to an estrogen-unresponsive tumor.

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