Interleukin 1 System and Sex Steroid Receptor Expression in Human Breast Cancer: Interleukin 1α Protein Secretion Is Correlated with Malignant Phenotype

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ABSTRACT

Purpose: The interleukin 1 (IL-1) system plays an important role in human pathology and is involved in the local control of malignant disease. However, little is known about its expression in breast cancer and its correlation with prognostic parameters such as receptor status and grading.

Experimental Design: The expression of IL-1α and other IL-1 family members was analyzed by reverse transcription-PCR, ELISA, and immunohistochemistry in breast cancer cell lines, tumor-derived fibroblasts, and breast cancer tissue biopsies and compared with sex steroid receptor status and grading.

Results: In breast cancer cell lines, IL-1α and -β gene expression was present in the phenotypically most malignant cell lines, whereas estrogen receptor (ER) α and progesterone receptor mRNA expression was confined to lines that exhibit a rather benign phenotype. Only the highly malignant receptor-negative tumor cell line MDA MB 231 expressed IL-1α protein, and none of the cell lines secreted IL-1β. Biopsies from breast cancer tissue expressed various amounts of IL-1α, IL-1β, and IL-1 receptor antagonist mRNA, but consistently high levels of IL-1R1. IL-1α protein expression was detected in tumor cells and/or adjacent stroma in 88%, and epithelial protein expression was correlated with both poor differentiation (P = 0.002; r = 0.469) and decreasing epithelial ERα expression (P = 0.004; r = -0.387). Furthermore, stromal IL-1α was predominant in areas with low or absent ERα protein expression in neighboring tumor epithelium (P = 0.001; r = -0.457).

Conclusion: We have demonstrated the presence of a functional IL-1 system in breast cancer and found that IL-1α is inversely correlated with local sex steroid receptor expression. We hypothesize that the unphysiological expression of IL-1α in less differentiated and ERα-negative tumors might contribute to their local invasiveness and malignant behavior.

INTRODUCTION

The IL-1 family of ligands and receptors is formed by functionally related proteins and consists of two ligands, IL-1α and IL-1β, which can be produced by a variety of cells, and by two different receptors, IL-1R1 and IL-1R1I, which are constitutively expressed in many different target cells. Whereas IL-1R1 is the functional signal-transducing receptor, IL-1R1I appears to act as a decoy receptor (1). The natural IL-1Ra and the soluble (s) IL-1 receptor forms sIL-1R1 and sIL-1R1I antagonize IL-1 biological activity and complete the family (2). IL-1α was first identified as a macrophage-derived lymphocyte-activating factor and has since then been shown to elicit a broad spectrum of biological activities in vitro and in vivo (3). It is mainly produced in mononuclear phagocytes but can also be released by various other cell types such as epithelial cells and keratinocytes (4).

Although IL-1α has been shown to be a critical cytokine in many aspects of human reproduction (5), its expression is generally considered to be associated with disease [for a review, see Dinarello (6)]. IL-1α is released by a number of solid tumors and serves as chemoattractant for lymphocytes that play a critical role in the malignancy-associated inflammatory responses (7). Its production by tumor cells results in an autocrine and paracrine induction of prometastatic genes in human breast cancer (8). IL-1α has been shown to induce several proteolytic enzymes such as MMP-1, MMP-2, MMP-3, and MMP-9 in breast stromal fibroblasts, suggesting a role in local extracellular matrix degradation and tumor invasion (9). IL-1-mediated signal transduction results in an up-regulation of the c-Fos/c-Jun complex (10), and c-Jun overexpression in the ER+ breast cancer

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cell line MCF-7 has already been demonstrated to lead to an overexpression of MMP-9 and a down-regulation of ER, which in turn causes an invasive and hormone-resistant phenotype (11). These observations provide a molecular basis for findings by Danforth et al. (12), who have previously shown that IL-1α is able to block estradiol-stimulated growth and to down-regulate the ER in MCF-7 cells in vitro.

Considering a potentially inverse correlation between IL-1 expression and cellular sex steroid receptor content, we have analyzed the gene expression of members of the IL-1 system and correlated it to ERα, ERβ, and PR mRNA expression in a panel of breast cancer cell lines, monocultures of stromal fibroblasts derived from malignant breast tumors, and breast cancer tissues of different grading. We have furthermore performed immunohistochemistry to locate the cellular source of IL-1α protein production in malignant breast tumors of different histology and grading.

MATERIALS AND METHODS

**Cell Culture and Tissue Specimen.** Primary cultures of stromal fibroblasts were established from surgical specimens that had been obtained from the malignant tumor of breast cancer patients as previously described (13, 14). Immunolabeling for vimentin and cytokeratin confirmed that the fibroblast monolayers did not contain contaminating epithelial cells. Epithelial breast cancer cell lines were purchased from the American Type Culture Collection (Manassas, VA), and were cultured in DMEM (MCF-7, MDA MB 231, SKBR3, ZR 75-1, and HS 578T) or RPMI (T47D), containing 5–10% FCS, 100 units/ml penicillin, 100 units/ml streptomycin, and 0.25 mg/ml amphotericin B (Life Technologies, Inc., Gaithersburg, MD). Cell culture experiments were performed in FCS-free medium after the culture plates were rinsed with PBS. Breast cancer tissue samples were obtained from surgical specimens of women undergoing lumpectomy or mastectomy for invasive breast cancer and were immediately snap-frozen in liquid nitrogen. Tissues were pulverized before resuspension in 4 M guanidine isothiocyanate, whereas cell cultures were directly harvested in guanidine isothiocyanate. The resulting cell lysates were then layered onto a CsCl cushion (5.7 M CsCl and 25 mM sodium acetate, pH 6.0) and centrifuged in a Beckman L8-60M ultracentrifuge (Beckman Coulter, Fullerton, CA) under conditions previously described (15). Pellets were ethanol precipitated, resuspended in an appropriate volume of ddH2O, and stored at −20°C. RNA concentrations were determined spectrophotometrically, and the quantity and quality of all samples were analyzed on denaturing 1% agarose minigels containing 200 μg/ml ethidium bromide. cDNA was synthesized by adding 0.8 μg of total RNA to 2.5 μl/μg murine leukemia virus reverse transcriptase (Life Technologies, Inc.), 2.5 μM random hexamers (Life Technologies, Inc.), 1 unit/μl RNase inhibitor (Promega, Madison, WI), 1 mM concentrations of each dNTP, 5 mM MgCl2, 500 mM KCl, and 100 mM Tris-HCl in a total volume of 20 μl and incubating them at 42°C for 15 min. The reaction was terminated by heating to 90°C for 5 min. In a subsequent step, a PCR amplification was performed in the same tube by adding 2.5 units of Taq polymerase (PerkinElmer Corp., Norwalk, CT) and 15 pmol of each primer in 80 μl of a 1.25 mM MgCl2, 50 μM KCl-10 mM Tris-HCl buffer. Primers were purchased from PerkinElmer Corp. (IL-1α, IL-1β), or from VBC Genomics, Vienna, Austria (IL-1RII, IL-Ra, ERα, ERβ, PR). Primer pairs were selected to span exon boundary sequences to avoid signal detection from genomic DNA. cDNA sequences, primer locations on the cDNA, and the sizes of the amplified fragments have been published previously (16–18). The reactions were conducted in a DNA Thermal Cycler 480 (PerkinElmer) under optimal cycling conditions. Horizontal 2% agarose gel electrophoresis was conducted in the presence of ethidium bromide solution (Sigma-Aldrich). After completion of electrophoresis, the agarose gel was photographed, and cDNA size calculation and densitometry were carried out by using the Molecular Analyst software (Bio-Rad Laboratories). The relative amount of gene expression of each parameter was then determined by comparison with coamplified β-actin.

**IL-1 ELISA.** Human IL-1α and IL-1β concentrations in tumor cell-conditioned medium were measured in microtiter plates by IL-1α and IL-1β immunoassays (R&D Systems, Minneapolis, MN) according to the manufacturer’s conditions. Absorbances were read in a TiterTek Multiscan MCC 340 spectrophotometer (Flow Laboratories). After completion of the experiments, tumor cells were harvested and counted in a Neubauer chamber culture and the amount of protein normalized to cell number.

**Immunohistochemistry.** Paraffin-embedded tissue sections were deparaffined, and endogenous peroxidases were inactivated by a 15-min treatment with methanol containing 3% hydrogen peroxide. After a short rinsing step in tap water, nonspecific binding was blocked with goat serum for 30 min, and the monoclonal mouse antihuman IL-1α antibody MAB 200 (R&D Systems) was added at a concentration of 1:50. ERα and ERβ were immunostained by using the monoclonal antihuman ERα antibody 1D5 (NeoMarkers, Fremont, CA), diluted 1:100, and the monoclonal antihuman ERβ antibody H-150 (Santa Cruz Biotechnology, Santa Cruz, CA), diluted 1:50.

All slides were incubated at 4°C overnight, washed in PBS for 5 min, and incubated with peroxidase-labeled dextran polymers conjugated to antimouse immunoglobulins (EnVision, DAKO Corp., Carpenteria, CA) for IL-1α and with a biotinylated and horseradish peroxidase-labeled secondary antibody (Immuno Cruz Detection Kit; Santa Cruz Biotechnology) in the case of ERα and ERβ. The sections were subsequently washed with PBS and subjected to diaminobenzidine for 10 min. The reaction was finished by rinsing in distilled water for 5 min. All slides were counterstained with Mayer’s hematoxylin, dehydrated, and mounted with DPX mounting medium (FLUKA, Buchs, Switzerland). Protein expression was semiquantified according to the IRS developed by Remmele et al. The IRS is the product of staining intensity (from 0 = no staining to 4 = strong staining) and percentage of positive cells (0 = 0% of cells stained; 1 = <10% of cells stained; 2 = 10–50% of cells stained; 3 = 51–80% of cells stained; 4 = >80% of cells stained). The IRS can range from 0 to 12 and values of >2 are considered positive (19).

**Statistics.** All statistical analyses were performed with the SPSS 10.0.1 software (SPSS, Inc., Chicago, IL).
IL-1 System and Sex Steroid Receptor Expression in Malignant Breast Tumors. The results of IL-1 system and sex steroid receptor gene expression in breast 48 cancer samples are shown in Table 1. IL-1α gene expression was detected in 40 cases (84%), with signal intensities varying greatly. IL-1β was found in 44 biopsies (92%) with variable amounts of mRNA expression. IL-1Ra mRNA was amplified in 35 cases (73%). The most consistent expression of any IL-1 family member was observed for IL-1RII, which was present in all biopsies (100%) and which was uniform regardless of tumor histology or grading. When ERα, ERβ, and PR gene expression was analyzed in the same tumor samples, we found high expression of ERα mRNA in 45 cancer tissues (94%), regardless of grading or histological subtype. Similarly, 45 tumor samples expressed PR mRNA (94%), with medium to high PR expression in 44 samples. In one case, PR mRNA was weak but clearly detectable. ERβ mRNA expression was detected in 34 breast cancer tissues (71%).

The amount of cytokine/hormone receptor gene expression was further normalized against β-actin mRNA expression, and classified into “no” (0), “little” (+), “intermediate” (+++), and “high” (++++) levels of mRNA expression (Fig. 3). Using nonparametric correlations, we found that the overall IL-1α gene expression was significantly correlated to IL-1β, IL-1Ra, and IL-1RII mRNA expression (Kendall τ-c: P = 0.029; r = 0.247, 95% CI: 0.036; r = 0.252, and P = 0.035; r = 0.263, respectively), thus suggesting the presence of a functioning IL-1 system in malignant breast tumors in vivo. Using the same statistical model, we also found that histological tumor grading was indirectly correlated to the amount of ERα and PR mRNA expression (Kendall τ-c: P = 0.025; r = −0.219, P < 0.0001; r = −0.365, respectively). Tumor grading, was, however, directly correlated to the amount of ERβ (P = 0.047; r = 0.171), which could suggest that poorly differentiated breast tumors are more likely to express higher levels of ERβ mRNA. Interestingly, tumor samples that expressed higher levels of ERβ mRNA were also likely to express more IL-1α mRNA (Kendall τ-c: P = 0.004, r = 0.317), thus indicating that IL-1α is associated with a more malignant phenotypical behavior of tumors.

IL-1α, ERα, and ERβ Protein Expression in Breast Cancer. Fig. 4 shows IL-1α, ERα, and ERβ protein expression as analyzed by immunohistochemistry in 16 human breast cancer tissues of different histological grading. The amount of expression was quantified by using a semiquantitative scoring.

When examining the IL-1α and IL-1β protein expression (Fig. 2), we were unable to detect secreted IL-1β protein in any of the conditioned media that had previously been exposed to the breast cancer cell lines analyzed, and only MDA MB 231 produced IL-1α (49 ng/ml/million cells/24 h).

All of the 15 tumor-derived but presumably “nonmalignant” fibroblast monocultures expressed easily detectable IL-1α, IL-1RII, and PR mRNA (Table 1, TF monocultures), and the majority also expressed IL-1β mRNA (73%). Gene expression for the IL-1Ra and the ERα was detected in 6 of 15 cases (60%). mRNA for the ERβ was, however, found in only three cases (20%). No apparent correlation was observed between the degree of gene expression and the histological grading of the original tumor sample in any of the fibroblast cultures analyzed (data not shown).
system (IRS) as described in “Materials and Methods.” Immunohistochemical staining results are described in Table 2, where an IRS of 0–2 was considered negative (−). An IRS of 3–5 was considered + (weak expression), an IRS of 6–9 was considered ++ (intermediate expression), and an IRS of 10–12 was considered +++ (strong expression).

IL-1α protein was detectable in both tumoral epithelium and surrounding stroma and was present in at least one of the two compartments in all G3 tumors and in the majority of G1 and G2 tumors. The amount of epithelial IL-1α protein expression was significantly correlated with histological grading in a way that poorly differentiated tumors would produce more IL-1α protein (P = 0.002, r = 0.469, Kendall τ test; and Fig. 4, A, D, and G). Although there was a clear correlation between epithelial and stromal IL-1α protein expression (P < 0.0001, r = 0.527), stromal IL-1α alone did not correlate with histological grading (P = 0.371, r = 0.188). As expected, ERα protein expression was prevalent in the malignant epithelium in tumors of higher differentiation, and was undetectable in any of the G3 tumors (P = 0.011, r = −0.735 and Fig. 4B, E, and H). In one case (case 101/01), tumoral epithelium (G2) remained negative, whereas histologically benign glandular epithelium in the vicinity showed weak staining. Similarly, ERβ protein production was more prominent in tumor cells of a more benign phenotype, although the receptor was also detectable in poorly differentiated (G3) tumors, albeit at a lower level of expression (P = 0.031, r = −0.281, and Fig. 4, C, F, and J). Neither ERα nor ERβ were immunodetectable in any of the stromal cells surrounding malignant epithelium.

When IL-1α protein expression was compared with ERα and ERβ distribution, we found a very significant inverse correlation between both epithelial and stromal IL-1α content and

| Table 1 IL-1 system and sex steroid receptor mRNA expression in human breast cancer (breast cancer tissues) and in monocultures of breast cancer-derived stromal fibroblasts (TF monocultures) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Breast cancer tissues | IL-1α | IL-1β | IL-1Ra | IL-1TLR | ERα | ERβ | PR |
| G1 (n = 4) | 4 (100) | 4 (100) | 4 (100) | 4 (100) | 4 (100) | 2 (50) | 4 (100) |
| G2 (n = 36) | 29 (81) | 32 (89) | 25 (69) | 36 (100) | 35 (97) | 24 (67) | 35 (97) |
| G3 (n = 8) | 7 (88) | 8 (100) | 6 (75) | 8 (100) | 6 (75) | 8 (100) | 6 (75) |
| Total | 40 (84) | 44 (92) | 35 (73) | 48 (100) | 45 (94) | 34 (71) | 45 (94) |
| TF monocultures | | | | | | | |
| Total | 15 (100) | 11 (73) | 9 (60) | 15 (100) | 9 (60) | 3 (20) | 15 (100) |

* Numbers in parentheses, percent.
ERα receptor expression \( (P = 0.004, r = -0.387, \text{ and } P = 0.001; r = -0.457, \text{ respectively}) \). However, no correlation was seen when tumoral IL-1α expression was compared with epithelial ERα \( (P = 1.000, r = -0.000, \text{ and } P = 0.236; r = -0.211, \text{ respectively}) \).

**DISCUSSION**

The role of the IL-1 system in human breast cancer is conflicting. IL-1 has been shown to inhibit growth of breast cancer cells and to promote cellular differentiation *in vitro*, but it is equally known to stimulate the expression of several proteolytic enzymes in human cancer \( (20–22) \). The consecutive degradation of extracellular matrix is a key element of local invasion and metastasis \( (23, 24) \).

Little is also known about the expression and role of IL-1α in the normal breast. Mice deficient (knockout) of IL-1α and IL-1β are born healthy and develop normally with the exception of an altered response to febrile responses in IL-1β knockout mice \( (25) \). Observations in other human tissues, however, indicate that this cytokine is a key inducer of MMPs release which, in turn, leads to the subsequent degradation of extracellular matrix proteins and local tissue remodeling \( (26, 27) \). Interestingly, in the human endometrium, where the IL-1 system has a key role in the induction of menstrual tissue shedding by MMP-1, its expression and secretion are highly regulated by sex steroids \( (28) \). The stringent control of IL-1α by sex steroid receptor action is, however, abrogated in malignant endometrial tumors, thus resulting in an increase of IL-1α secretion especially in dedifferentiated cancers \( (29) \). This observation, although obtained from endocrine-responsive tumors of another entity, fits well our finding of IL-1α mRNA being confined to sex steroid receptor-negative breast cancer cell lines. In fact, we noted a very strong inverse correlation between IL-1α gene expression and ERα and PR mRNA expression \( (P = 0.007 \text{ and} \)
P < 0.0001, respectively), and of the nine breast cancer cell lines analyzed, only the ERα-PR- cell line MDA MB 231 was able to secrete IL-1α. This is also in accordance with findings by Bhat-Nakshatri et al. (30), who observed that NF-κB activation and IL-6 production could be induced by conditioned medium from ER− but not from ER+ breast cancer cell lines. A survey of cytokines known for their ability to induce NF-κB identified IL-1α as the factor responsible for NF-κB activation in fibroblasts. In contrast, it has been shown previously that IL-1α blocks estradiol-stimulated growth and down-regulates the ER in MCF-7 breast cancer cells in vitro (12). Our finding of IL-1RtI gene expression in all but one tumor cell line would then suggest that the release of IL-1α by tumor cells is involved for the down-regulation of local ERα expression through an autocrine feedback loop via IL-1RtI. Although the lack of ERα expression in tumor cells is usually indicative of a more malignant phenotype, it cannot be excluded that the down-regulation of ERα by IL-1α might also represent some sort of a beneficial self-defense mechanism that is aimed at preventing overstimulation by local sex steroids.

Because tumor cells eventually need surrounding stroma and vascular elements to grow and to survive, stromal fibroblasts are usually involved in the complex intercellular signaling between tumor cells and their environment. We have therefore also investigated the expression pattern of the IL-1 system in these cells and found IL-1β and IL-1Ra to be expressed in almost all mononucleotides. IL-1α, IL-1RtI, and PR mRNAs were even detected in 100% of tumor-derived fibroblasts. The same cultures, however, expressed considerably less ERα and ERβ. It is unclear whether their limited expression is caused by a down-regulation through a cell culture-associated release of IL-1α or simply is part of the phenotype of tumor-derived fibroblasts.

In contrast to breast cancer cell lines and fibroblastic mononucleotides, tumor tissues are composed of a complex and heterogeneous system of various cell types, and mRNA extracted from frozen sections of whole tumors cannot account for a spacial expression pattern of specific genes. Taken into consideration, the abundance of IL-1α and sex steroid receptor-expressing cells in breast tissue and the relatively high sensitivity of RT-PCR, is therefore not surprising that we have detected IL-1α, IL-1β, IL-1Ra, and IL-1RtI mRNA in the vast majority of tumor samples and that we were unable to find a correlation between IL-1α gene expression and tumor differentiation. Nevertheless, because all major members of the IL-1 system were detectable in most of the samples, our findings clearly indicate the existence of a functional autocrine/paracrine IL-1 system in breast cancer.

To investigate the spatial expression of IL-1α protein, we performed immunohistochemical analysis on invasive ductal breast tumors of different histological grading. ERα and ERβ immunostaining was also done on consecutive serial tissue sections to detect potential correlations between cytokine release and sex steroid receptor protein expression. We observed a clear correlation between epithelial IL-1α production and histological grading in a way that poorly differentiated tumors produce more IL-1α protein (Table 2; P = 0.002, r = 0.469). To our knowledge, this is the first description of an association between IL-1α protein expression and histological tumor grading. Furthermore, IL-1α protein expression was indeed found to be inversely correlated to ERα, and epithelial and stromal L-1α protein expression was confined to areas devoid of ERα (P = 0.004, r = −0.387, and P = 0.001, r = −0.457, respectively). These observations are supported by several publications describing a mutual down-regulation between IL-1α and ERα: IL-1α inhibits MCF-7 growth in a dose-dependent way, an effect that can almost totally be overcome by the addition of 17β-estradiol (31). Conversely, IL-1 in combination with IL-6 is able to additively inhibit growth in the presence of stimulatory functions.

Table 2 Immunohistochemical analysis of IL-1α, ERα, and ERβ in human breast cancer

<table>
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* Histology for all samples was invasive ductal.

b −, no expression; +, weak expression; ++, intermediate expression; ++++, strong expression as assessed by the IRS (0−2 = −; 3−5 = +; 6−9 = ++; 10−12 = +++).

c Normal ductal glands positive, tumor cells negative.
estradiol, and IL-1 alone is sufficient to down-regulate the ER content of MCF-7 cells in vitro (32).

Taking the facts together, we have shown that IL-1α expression in breast cancer cell lines and in malignant breast tumors is associated with both, a more malignant phenotype and ERα negativity. Because IL-1α is a potent stimulator of tissue-degrading proteases, we hypothesize that the release of IL-1α from tumor cells could have a significant role in local tissue degradation invasiveness. Neutralization of IL-1α by antibodies or synthetic IL-1 receptor antagonists might therefore eventually turn out to become an effective treatment option especially in more aggressive forms of breast cancer.

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