The Urokinase Receptor Is Expressed in Invasive Breast Cancer but not in Normal Breast Tissue


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Abstract

We have studied expression of the urokinase receptor (u-PAR) in paraffin-embedded breast tissues at various stages of malignant progression. Forty-nine of 59 invasive cancers studied showed varying degrees of reactivity with our polyclonal antibody. The staining pattern was variable from case to case, although strong surface staining of tumor-associated macrophages was evident in most of these sections. In several cases, blood vessels in selected tumor areas were stained, as confirmed by treatment of adjacent sections with an anti-factor VIII antibody. These could represent regions of recent angiogenesis. Staining of tumor cells was observed in 21 of 59 cases and was extensive in 5 cases but confined to a small percentage of cells in the remaining 16 samples. In contrast with the cancer sections, all normal breast tissue (12 cases) was negative, as well as all fibroadenomas (4 cases), papillomas (5 cases), and hyperplasia with atypia (2 cases) studied. Seven carcinomas in situ examined were also negative for u-PAR, with the exception of few macrophages in two cases, suggesting that u-PAR expression may be associated with invasive tumor. The presence of u-PAR in human breast cancer and its absence from nonmalignant breast tissue supports the idea that plasminogen activation plays an important role in the process of cancer invasion. Expression of u-PAR on macrophages, endothelial cells, and cancer cells suggests the existence of complex paracrine interactions between tumor cells and stroma.

Introduction

Proteolytic enzymes that degrade the ECM2 play an important role in the processes of cancer invasion and metastasis (1, 2). u-PA is a serine protease that activates plasminogen to plasmin, which itself displays proteolytic activity against several components of the ECM, such as laminin, fibronectin, and collagen. Plasmin is also capable of activating other procollagenases, giving origin to a broad, proteolytic cascade. A cell surface receptor for u-PA has recently been identified and cloned (3–5). Binding of u-PA to its receptor, u-PAR, not only increases u-PA enzymatic activity (6) but may also enable cells to exercise a focal and directional proteolysis of the ECM (7). Both in vitro and animal model data have shown the importance of u-PAR in invasion and in metastasis (8–10). Furthermore, increased production of u-PAR has been detected in breast cancer, compared to normal mammary tissue and benign breast disease (11, 12). Elevated levels of u-PAR in breast cancer samples have been correlated to reduced relapse-free and overall survival (13–15).

In the present study, we have established an immunohistochemical assay to detect the expression of the u-PAR in formalin-fixed, paraffin-embedded specimens. We have used this assay to examine the distribution of u-PAR in breast tissue at various stages of malignant progression and to compare it to u-PAR expression by nonmalignant breast tissue.

Materials and Methods

Cell Cultures. Breast cancer cell lines and the human histiocytic lymphoma cell line U937 were acquired from the American Type Culture Collection (Rockville, MD) and propagated in the recommended medium supplemented with 10% fetal calf serum. U937, a variant of U937 that shows no binding for u-PA (16), was obtained from O. J. Finn (Duke University, Durham, NC). Before inclusion in paraffin, U937 and I937 were cultured for 3 days in medium supplemented with 10 ng/ml phorbol 12-myristate 13-acetate (Calbiochem). Normal breast epithelial cell cultures and fibroblast cultures were obtained as described previously (17).

For inclusion in paraffin, cultured cells were rinsed several times in PBS, removed from the flasks by scraping with a rubber policeman, and pelleted in glass centrifuge tubes which had been previously coated with a layer of collodion (Fisher Scientific, Pittsburgh, PA). The collodion tube containing the cell pellet was then removed and processed for paraffin embedding by the Clinical Pathology Laboratory of UCSF.

Immunofluorescence and Immunohistochemistry. A mouse monoclonal antibody (anti-Mo3f) and an affinity-purified rabbit polyclonal directed against the human urokinase receptor were obtained as described previously (18, 19). For immunofluorescence assays, cells were grown on glass coverslips, fixed in 10% buffered formalin, and incubated for 30 min at RT with either the primary antibody (1:100 dilution) or an isotype-matched, irrelevant control antibody (Zymed, South San Francisco, CA), followed by a 20-min incubation with the fluorescein-conjugated secondary antibody (Vector, Burlingame, CA). Coverslips were mounted in 10% PBS-glycerol and examined under a BH-2 Olympus microscope.

For immunohistochemistry assays, routinely processed formalin-fixed and paraffin-embedded tissues were obtained from the Pathology Department of UCSF, and alcohol-formalin fixed samples were obtained from the Pathology Department of the California Pacific Medical Center (San Francisco, CA). After dewaxing in xylene and rehydrating, 5-μm sections were treated with 0.05% trypsin at 37°C for 15 min, blocked with 20% normal goat serum, and incubated with the polyclonal anti-u-PAR serum (concentration ranging from 5 to 15 μg/ml) for 1 h at RT. Blocking for endogenous peroxidase activity was performed by incubation in 0.03% hydrogen peroxide for 10 min at RT, followed by incubations with biotin goat anti-rabbit (1:400) for 30 min at RT, then with horseradish peroxidase (HRP)-streptavidin (1:70) for 20 min at RT, and color development with hydrogen peroxide-activated diaminobenzidine for 5 min. Slides were counterstained with hematoxylin, dehydrated, and mounted. All dilutions were done in PBS with 0.1% bovine serum albumin. Slides were washed between steps in PBS with 0.1% Triton X-100. Normal horse serum, normal goat serum, and biotin-conjugated goat anti-rabbit antibodies were purchased from Vector. HRP-streptavidin was from Biocytex (San Ramon, CA). Bovine serum albumin, Triton X-100, and diaminobenzidine were from Sigma Chemical Co. (St. Louis, MO).

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2 The abbreviations used are: ECM, extracellular matrix; u-PA, urokinase-type plasminogen activator; u-PAR, urokinase receptor; iu-PA, recombinant, soluble urokinase receptor; PBS, phosphate-buffered saline; UCSF, University of California, San Francisco; RT, room temperature; PCR, polymerase chain reaction; cDNA, complementary DNA; CHO, Chinese hamster ovary cells.
Staining for blood vessels and for leukocytes was performed similarly by the Immunopathology laboratory at UCSF using a polyclonal rabbit anti-human factor VIII from Dako (Carpinteria, CA) and a mixture of monoclonal antibodies against the leukocyte common antigen CD45 (Dako and Biogenex), respectively. Specific staining of macrophages was performed with a monoclonal antibody against CD68 (Dako) following an identical protocol.

Reverse Transcription and PCR Amplification. Total cellular RNA for reverse transcriptase-PCR was isolated by lysis in guanidinium isothiocyanate and purified by CsCl ultracentrifugation. One μg of total RNA from each sample was reverse transcribed using Moloney murine leukemia virus reverse transcriptase (BRL, Rockville, MD) and 25 ng/μl of oligodT primer (Promega, Madison, WI) according to the supplier’s protocol. As a control for the absence of genomic DNA, reactions run in the absence of reverse transcriptase revealed no amplified product. Five % of the cDNA product was amplified in a Programmable Thermal Controller (M.J. Research, Watertown, MA) for a total of 30 cycles consisting of 45 s at 95°C, 25 s at 55°C, and 3 min at 72°C. MgCl₂ was added to a final concentration of 1.5 mM in this reaction. Taq Polymerase was obtained from Perkin Elmer Cetus and used according to the supplier’s instructions. The following primers were based on the published u-PAR sequence (5) and synthesized by the Biochemical Resource Center at UCSF.

u-PAR sense: 5'-TTCTCAGGTTTCTCTTTGGTAC-3'
u-PAR anti-sense: 5'-GCCCTAGGACATGGTGTCAC-3'

An aliquot of the PCR product was then electrophoresed on a 1% agarose gel along with size markers. The expected amplification product was 1207 base pairs. Control reactions were performed, following an identical protocol, with primers for β-actin (Clontech, Palo Alto, CA). To control for the possibility of exogenous contaminant DNA, reactions were performed substituting water for the cDNA substrate. No amplified product was obtained under these conditions.

Production of Recombinant Soluble u-PAR. A recombinant form of the u-PAR cDNA encoding the full length protein was cloned by PCR using U937 cDNA as template and the primers given above (20). In this reaction, the MgCl₂ concentration was 1.5 mM, and 30 cycles of amplification were performed as follows: 94°C × 1 min, 53°C × 2 min, and 72°C × 3 min. The resulting 1.2-kilobase fragment was digested with XhoI and HindIII and cloned into the corresponding sites in BluescriptSK (Stratagene, La Jolla, CA) to generate pSkuuPAR. In a second round of PCR, pSkuuPAR was used as the template to introduce a stop codon after Arg281, deleting the putative phosphoside linkage site. Reaction conditions were similar to those used for the initial cloning except that the MgCl₂ concentration was 2.5 mM. The following primers were used:

Sense: 5'-ATAGGGCGAATGGGTACC-3'
Antisense: 5'-CTGGATGTCCAGTACCGCTAGTCTAGACC-3'

The resulting 957-base pair fragment was cloned into pCR1000 (Invitrogen, San Diego, CA), subsequently excised with KpnI and NotI, and re-cloned into the corresponding sites of the expression vector pCEP (Invitrogen) to yield pCPE-Trunc. A stable cell line expressing truncated u-PAR was obtained by transfection of CHO with pCPE-Trunc using the calcium phosphate method (21). Serum-free conditioned media were prepared, concentrated 10-fold on a YM-30 membrane (Amicon, Danvers, MA), and collected by affinity chromatography on u-PA-Sepharose. Bound u-PAR was eluted with acid-glycine as described (20), and the neutralized eluate was concentrated using a Centricon 30 micro-concentrator prior to use. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis followed by silver-staining showed a single, broad band centered at approximately Mₐ 50,000–55,000 which reacted with polyclonal anti-u-PAR antisera.

Metabolic Labeling and Immunoprecipitation. Metabolic labeling and immunoprecipitation of CHO cells expressing u-PAR were performed essentially as described (20). Briefly, u-PAR protein was collected by immunoprecipitation using the rabbit polyclonal anti-u-PAR antisera (1:100) followed by protein A-Sepharose. In some experiments, u-PAR was also collected from labeled conditioned media by addition of u-PA-Sepharose. Beads were washed, and labeled protein eluted exactly as described for immunoprecipitation (20).

Results

Expression of the Urokinase Receptor in Cultured Cells. We examined several breast cancer cell lines for expression of the urokinase receptor using an indirect immunofluorescent assay. Most cell lines reacted with the u-PAR antibodies, although the percentage of positive cells varied greatly among the different cell lines. Cell lines which were positive by this analysis included MDA-MB-435 (20% positive cells), SKBR-3 (25% +), BT-549 (25–40% +), MDA-MB-231 (75% +), and MDA-MB-468 (80–100% +). MDA-MB-134, CAMA-1, and BT-474 cell lines were negative. Comparable results were obtained with the monoclonal and the polyclonal antibodies. In addition to the cancer cell lines, we studied normal breast epithelium cultures (three samples) and fibroblast cultures (three samples) for u-PAR expression. All showed distinct surface staining for u-PAR on a large percentage of cells (75–100%). No staining was observed when the assay was performed using isotype-matched control antibodies or nonimmune serum and when the primary antibody was omitted.

Expression of the u-PAR protein, as assessed by immunofluorescence, was consistent with the detection of u-PAR mRNA by reverse-transcriptase PCR. The amplification product showed a band of the expected 1207-base pair size only in the six cancer cell lines which were positive by immunofluorescence (results for SKBR3, MDA-MB-468, BT-374, and MDA-MB-134; Fig. 1). cDNA prepared from all normal epithelium and fibroblast cultures also yielded an amplification product for u-PAR. β-Actin cDNA could be amplified from all samples, indicating that the mRNA was of adequate quality.

Immunohistochemical Detection of u-PAR in Paraffin-embedded Cultured Cells. After characterization for u-PAR expression, the breast cancer cell lines were used as controls to develop an immunohistochemical assay for formalin-fixed, paraffin-embedded clinical specimens. To this end, the cells were collected by scraping and centrifugation, and the cell pellets were then fixed in formalin and embedded in paraffin, following the routine procedures of the clinical pathology laboratory at UCSF. Sections of the paraffin-embedded cell lines were stained using an immunoperoxidase method. The monoclonal antibody failed to detect u-PAR expression under these conditions; however, a clear signal was obtained using the polyclonal antisera on sections prepared from u-PAR-expressing cell lines (Fig. 2a). The u-PAR-positive cell lines showed both a surface and, in some cases, an intracellular distribution of the antigen, mainly in the perinuclear area. The percentage of breast cancer cells staining in the paraffin-embedded sections was slightly inferior to the fraction stained.

![Fig. 1. Detection of u-PAR mRNA in cultured normal and tumor breast epithelium by reverse-transcriptase PCR](image-url)
Fig. 2. Immunohistochemical detection of u-PAR in breast cancer. The rabbit polyclonal antiserum yields a distinct surface pattern on selected cells of the paraffin-embedded MDA-MB-435 breast cancer cell line (a). Staining is abolished by preincubation of the antibody with soluble recombinant u-PAR (b). In several invasive carcinomas, staining was confined to stromal cells (c) and was abolished by preincubation of the antibody with soluble u-PAR (d). In 16 of 59 cases, a small proportion of the cancer cells displayed surface staining for u-PAR (e). Many of the positive stromal cells were tumor-associated macrophages (f and g). Intraductal histiocytic cells also reacted strongly (e). Expression of u-PAR on blood vessels was confirmed by staining of adjacent sections with anti-u-PAR (g) or anti-factor VIII (h) antibodies, showing that the same structures reacted with both antibodies. In 5 of 59 samples, staining of cancer cells was extensive, and it displayed both a cytoplasmic and surface pattern (i). Bars. 50 μ (a-f), 25 μ (g-h), and 65 μ (i).
yielding a single, broad band centered at \( M_r 50,000 \) (Fig. 3). We incubated the polyclonal antibody with excess ru-PAR for 18 h at 4°C to allow saturation of the antigen binding sites. The antibody-receptor mixture was then used to replace the primary antibody in the immunoperoxidase assay. Under these conditions, all u-PAR-expressing cell lines tested (U937, MDA-MB-435, and SKBR3) showed no staining (compare Fig. 2, a and b, for MDA-MB-435).

**Immunohistochemical Localization of u-PAR in Breast Tissues.**

We studied 59 cases of invasive carcinoma for expression of u-PAR (Table 1). The staining pattern varied greatly from case to case from just a few scattered, positive cells to extensive staining of most of the section and was often heterogeneous within the same sample. Blocking of the antibody with ru-PAR was used as a specificity control for staining of the tissue sections. Preincubation of the antibody with the soluble receptor effectively abolished staining (Fig. 2, c and d). In addition, no staining was obtained when nonimmune rabbit serum was substituted for the anti-u-PAR antibody.

In most cases, staining was confined to cells within the stroma. Cells with macrophage morphology showed an intense surface distribution of the antigen (Fig. 2f). Such cells were often visible in areas of necrosis and at the periphery of the tumor mass and sometimes within fat lobules. Presence of a leukocyte infiltrate and, specifically, of macrophages in these locations was confirmed by staining of an adjacent section with antibodies directed against the leukocyte common antigen, CD45, or the macrophage-specific marker, CD68 (not shown). In a few cases, staining of lymphocytic cells within such infiltrates was evident. Such cells were CD45 positive but negative for CD68 on an adjacent section.

In 8 of 59 cases, u-PAR expression was localized to tumor-associated blood vessels, as confirmed by staining of adjacent sections with an anti-factor VIII antibody (Fig. 2, g and h). The pattern of vessel staining was very heterogeneous with several areas of reactivity in three cases and only occasional positive vessels in the remaining five cases.

Reactivity of cancer cells with the anti-u-PAR antibody was detected in a total of 21 of 59 cases. Prominent staining of the cancer cells was seen in only five cases (Fig. 2i). In the remaining cases, staining was limited to a small fraction of the cancer cells. In a few samples with areas of comedo-type morphology, clusters of cells within a tumor nodule showed either a distinct surface pattern (Fig. 2e) or intracellular staining concentrated in the proximity of the nucleus. Intraductal cells and material were often positive (Fig. 2e). Many intraductal cells had morphological features of foam cells, which have been shown to display histiocytic markers.3

Of the seven samples of ductal carcinoma in situ examined, only two showed staining of a small number of macrophages. Staining of blood vessels and epithelial cells was not observed in any carcinoma in situ. Two cases with areas of hyperplasia with atypia were completely negative. All benign lesions including fibroadenomas (four cases) and papillomas (five cases) were also negative, with the exception of occasional macrophages in two cases. We also studied several samples of normal breast tissue, obtained from reduction mammoplasties (three cases), negative biopsies (six cases), or from mastectomies (five cases). All normal tissue was negative for u-PAR, with the exception of some intraductal foam cells.

**Discussion**

In this paper, we show that u-PAR is expressed in human breast cancer but not in normal breast tissue or benign breast disease. In cancer tissue, u-PAR is present on a variable number of tumor cells and also on cells within the stroma. u-PAR-expressing stromal cells appear to be mostly macrophages and endothelial cells, based on staining of adjacent sections for leukocyte and endothelial markers. This finding is of interest in view of the complex interactions between tumor cells and the stromal environment. Endothelial cells in vitro have been shown to bear the receptor on their surface and to modulate receptor expression in response to treatment with various angiogenic factors (22–25). It is noteworthy that, in breast cancer, u-PAR is not present on all endothelium but only on blood vessels in selected areas and only in a fraction of the samples studied. These areas could represent regions of recent or ongoing vascularization since transient expression of components of the u-PA system in vivo has been correlated with angiogenesis during neovascularization of ovarian follicles, the corpus luteum, and the maternal decidua (26).

**Table 1 Expression of u-PAR in vivo and in cultured breast cells**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>No. cases positive/total cases</th>
<th>Vessels</th>
<th>Cancer cells*</th>
<th>Stromal macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vivo tissues</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>49/59</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>26 cases</td>
<td></td>
<td></td>
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<tr>
<td>14 cases</td>
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<tr>
<td>2 cases</td>
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<td>+</td>
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<tr>
<td>6 cases</td>
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<td>+</td>
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<tr>
<td>1 case</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Normal breast</td>
<td>2/7</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Normal mammary epithelium</td>
<td>0/4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilloma</td>
<td>0/4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cultured cells†</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal mammary epithelium</td>
<td>3/5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary carcinoma cell lines</td>
<td>6/9†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary fibroblasts</td>
<td>3/3</td>
<td></td>
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</table>

* Fraction of positive cells ranged between 1–5% in all cases except for 5 samples, where 30–80% of cells stained positively.
† Paraffin-embedded sections were stained by the biotin-streptavidin immunoperoxidase method.
‡ Cells cultured on glass coverslips were analyzed by indirect immunofluorescence.
§ Fraction of positive cells ranged from 20 to 100% (see text for details).

3 A. Thor, unpublished observation.

![Fig. 3. ru-PAR binds to u-PA and is recognized by anti-u-PAR rabbit antiserum. CHO cells expressing a soluble, truncated form of u-PAR were prepared and metabolically labeled as described in “Materials and Methods.” Lane 1, the expected Mr 50,000–55,000 protein product obtained following immunoprecipitation with anti-u-PAR antiserum. Lane 2, the product collected following incubation with u-PA-Sepharose. Electrophoresis was performed using an 8% sodium dodecyl sulfate-polyacrylamide gel electrophoresis under nonreducing conditions.](image-url)
Macrophages are a rare finding in normal breast tissue but were present in large numbers in several cancer specimens and were particularly prominent at areas of necrosis and at tumor margins. These cells stained strongly for u-PAR and could play a role in ECM breakdown and reabsorption at sites of tumor invasion. Paracrine interactions between tumor-infiltrating macrophages and cancer cells could result in increased cell-mediated plasminogen activation and invasiveness at the tumor margin. This idea is consistent with studies suggesting that tumor-infiltrating macrophages may act to promote tumor growth and metastasis (27).

Although in most cases lymphocyte infiltrates were negative, in a few samples, cells with lymphocytic morphology stained strongly for u-PAR. In an adjacent section, these cells were positive for the common leukocyte marker CD45 and negative for the macrophage-specific marker CD68. This data is consistent with the observation that in vivo and in vitro activated T-lymphocytes express detectable amounts of surface u-PAR.

Ten of the invasive carcinoma samples studied were completely negative for u-PAR expression. Although these cases may express u-PAR at levels below the sensitivity threshold of our assay, they could, however, represent a subset of tumors with scarce expression of the plasminogen activator system (and possibly more favorable prognosis). A study designed to examine the prognostic significance of u-PAR expression will establish the meaning of this negative subset.

The results we obtained on tissue samples differ somewhat from our observations of cultured cells. In particular, normal cultured breast epithelium expressed detectable u-PAR protein by immunofluorescence and u-PAR mRNA by PCR. The absence of u-PAR expression by normal epithelium in vivo could be related to the quiescent state of these cells, in contrast to the proliferative state induced by in vitro culture conditions. In this regard, it is noteworthy that the same normal epithelium cultures also produced detectable amounts of u-PA,5 while cell lysates from normal breast tissue have been reported to contain negligible levels of u-PA antigen when screened by enzyme-linked immunoassay (12, 13). This observation is consistent with a general up-regulation of the plasminogen activation system in normal tissue under in vitro culture conditions.

Our description of u-PAR expression in invasive breast carcinoma is consistent with the recent report by Pyke et al. (28). Using monoclonal anti-u-PAR antibodies, these investigators also detected expression of u-PAR by macrophages, cancer cells, and, in two cases only, endothelial cells. Using our antibody preparation, we were able to detect u-PAR expression on endothelial and cancer cells in a significantly larger fraction of samples. In particular, we observed several cases (16 of 59) in which only a small number of cancer cells (1–5%) expressed u-PAR (Table 1), in addition to samples (5 of 59) in which staining of cancer cells was more extensive. In their study, Pyke et al. (28) describe only cases (5 of 40) in which most or all cancer cells were positive. Our results suggest that the polyclonal antibody we used might be a more sensitive reagent; in this regard, it is noteworthy that our antibody preparation specifically recognizes multiple forms of u-PAR, including glycosylated and nonglycosylated forms and both free u-PAR and u-PAR complexed to u-PA (29). Whether the fraction of positive tumor cells carries prognostic significance will be shown by future studies correlating u-PAR staining with other prognostic and outcome variables.

Although it is difficult to establish with certainty that the antibody preparation used in these studies has no significant reactivity in addition to authentic u-PAR epitopes, several pieces of evidence support this conclusion: (a) immunoreactivity could be removed completely by preabsorption of the antibody preparation with excess purified u-PAR; (b) immunoprecipitation experiments using cultured breast cancer cell lines known to be positive for u-PAR expression showed a single, specific band at a molecular weight of approximately Mr 60,000–65,000; and (c) the overall similarity of our results with those obtained using anti-u-PAR monoclonal antibodies (28) suggests that the same antigen is being detected by our antibody reagent.

In addition to our analysis of invasive breast cancer, we also studied u-PAR expression in benign breast disease and in situ carcinomas. This is the first report to address this question. All papillomas and fibroadenomas tested were negative for u-PAR expression, with the exception of extremely rare macrophages in two cases. In addition, two samples containing areas of hyperplasia with atypia, considered to be a precancerous lesion, showed no u-PAR expression. All in situ carcinomas analyzed were negative for u-PAR, with the exception of a small number of macrophages in two samples. These data suggest that u-PAR expression by endothelial and cancer cells is limited to actively invasive disease.

The presence of u-PAR in human breast cancer, in contrast to its absence in nonmalignant breast tissue, adds to the evidence of the importance of cell surface plasminogen activation in human cancer. The development of pharmacological reagents that interfere with this process may provide us with a novel therapeutic approach to invasive disease. In addition, the presence of u-PAR in selected breast cancer cases may prove to be a useful indicator of prognosis. We are now using our immunohistochemical assay to investigate the correlation between patterns of u-PAR expression and breast cancer progression and long-term outcome. We are also developing new anti-u-PAR antibody reagents, such as those specific for the uPA-uPAR complex, which may prove to be even more powerful prognostic tools.

References


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