Prognostic Significance of Transforming Growth Factor β Receptor II in Estrogen Receptor-Negative Breast Cancer Patients

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ABSTRACT

Purpose: The role of transforming growth factor β (TGF-β) in breast cancer is ambiguous; it can display both tumor suppressor and enhancing effects. Activation of the TGF-β signal transduction system is subject to hormonal regulation. This study was conducted to further analyze the role of TGF-β receptors in breast cancer and to evaluate their significance as prognostic markers.

Experimental Design: Expression of TGF-β receptor I (TβRI) and TGFβ receptor II (TβRII) was retrospectively analyzed by immunohistochemistry in 246 breast cancer patients.

Results: Expression of TβRI was strongly correlated with tumor size (P < 0.001) and nodal status (P = 0.012) but only weakly with overall survival (P = 0.056). In contrast, TβRII was prognostic for overall survival in univariate analysis (P = 0.0370). In estrogen receptor (ER) -negative patients TβRII expression was correlated with highly reduced overall survival (P = 0.0083). In multivariate analysis TβRII proved to be an independent and highly significant prognostic marker with a hazard ratio of 6.8. Simultaneous loss of both ER and TβRII was associated with longer overall survival times comparable with those of ER-positive patients.

Conclusions: The results of this exploratory study show that TβRII is an independent, highly significant prognostic indicator for overall survival in ER-negative patients. In addition our results are supportive of a mechanism of breast cancer progression in which a selective loss of the tumor inhibitory action of TGFβ takes place, whereas tumor-promoting aspects remain intact.

INTRODUCTION

Breast cancer is the most common malignancy in women of the Western world. Generally accepted prognostic factors are nodal status, tumor size, and tumor grading. Moreover, breast tumors can be classified as either estrogen receptor (ER) positive or ER negative. The presence of ER is correlated with a better prognosis and predicts for response to antiestrogen treatment. Tamoxifen is currently the most frequently used endocrine therapy for ER-positive breast cancer patients (1). We have shown previously that the action of tamoxifen is at least partially mediated through activation of transforming growth factor-β (TGF-β; Refs. 2–6).

TGF-β is a pleiotropic growth factor, which affects many different cell functions such as proliferation, extracellular matrix synthesis, and immune responses (7).

TGF-β signals are mediated by specific transmembrane receptors. TGF-β receptor type I and II (TβRI, TβRII) are serine-threonine kinases, which form a heteromeric signal transduction complex upon ligand binding. TβRII phosphorylates TβRI, which activates TβRI kinase and initiates downstream signaling (8). Expression of TβRII is hormonally regulated, but expression of TβRI is not (9).

Conflicting data exist about the influence of TGF-β on the development and progression of breast cancer. TGF-β is a very potent inhibitor of primary human mammary epithelial cells, and most human breast cancer cell lines are growth inhibited by TGF-β as well (10, 11). However, in later tumor stages TGF-β appears to become a promoter of progression (12, 13), and stimulation of angiogenesis, induction of extracellular matrix degradation, or the inhibition of antitumor immune responses prevail over the inhibitory effects on proliferation.

Loss of expression or functional inactivation of TβRI or TβRII leads to resistance against TGF-β (14, 15). Furthermore, defects in downstream signaling components have been associated with altered sensitivity to TGF-β and tumor progression in different tumor types (16, 17).

However, the clinical implications of such findings are still unclear. Therefore, in a retrospective immunohistochemical study we analyzed the correlation of TβRI and TβRII expression with overall survival in 246 breast cancer patients with a median follow-up of 5.7 years. To discriminate between hormone-dependent and -independent effects patients were additionally stratified for their ER status.

Our results show that expression of TβRII is correlated with poor prognosis and represents an independent prognostic marker in the subgroup of ER-negative patients.

MATERIALS AND METHODS

Patients. Paraffin-embedded primary tumors of 246 breast cancer patients were obtained from the archives of surgical pathology of the Robert Bosch Hospital (Stuttgart, Germany). The median age was 55 years (range, 26–88). Histolog-
ical typing showed 196 ductal invasive breast tumors, 25 lobular invasive and 25 tumors of miscellaneous type (medullar, inflammatory, or mucinous). The median follow-up was 5.7 years (range, 2 months to 15.3 years). Tumor staging was performed according to the Tumor-Node-Metastasis classification system, and histological typing was done according to WHO guidelines (18). ER and progesterone receptor (PR) were analyzed by either immunohistochemistry or the charcoal dextran method. ER and PR were classified as positive when either 15 fmol/mg protein or an immunoreactive score ≥2 was reached (19). Of the 246 patients 148 were classified as ER positive and 87 as ER negative. There were 142 PR-positive patients and 92 PR negative.

All of the patients had initially undergone either mastectomy or a breast-conserving resection of their primary carcinomas. There were 166 patients being treated in the adjuvant setting, and 44 received palliative treatment after relapse. Adjuvant treatment with tamoxifen was given to 71 patients, 49 patients received adjuvant treatment with cyclophosphamide, methotrexate and fluorouracil, 46 with anthracycline regimes (either mitoxantrone and cyclophosphamide; fluorouracil, doxorubicin and cyclophosphamide; or bonnadonna regimen), and 91 patients were treated with radiation. The sum of all treatments is >166, as some patients received more than one treatment.

**Antibodies and Immunohistochemical Method.** Affinity-purified rabbit polyclonal antibodies raised against TβRI (R-20) and TβRII (C-16; Santa Cruz Biotechnology, Inc., Heidelberg, Germany) were used for immunostaining of the tissues. Both antibodies were used previously for immunohistochemical studies by other groups (20–23).

Sections of 3 μm were prepared from the paraffin block of each patient tumor. The tissue sections were deparaffinized and rehydrated in descending alcohol dilutions. Before staining on a TechMate instrument (Dako, Glostrup, Denmark) the tissue sections were subjected to antigen retrieval in microwave oven using a citrate buffer solution (Dako). Endogenous biotin, biotin receptors, or avidin binding sites present in the tissue were blocked using an Avidin/Biotin Blocking kit (Vector Laboratories, Inc., Burlingame, CA). Endogenous peroxidase activity served for menopausal and PR status. No correlation was observed (Table 2).

Multivariate analysis in the subgroup of ER-negative patients was performed using Cox regression analysis in a model, which included tumor size, nodal status, distant metastases, and grading.

Differences in the TGF-β receptor expression between normal and tumor tissues, and associations between TGF-β receptor expression and other parameters such as tumor size, nodal status, grading, and hormonal status were assessed by χ² or Fisher's exact-test.

**RESULTS**

**Characteristics of the Patients.** Kaplan-Meier survival curves were calculated to evaluate the prognostic value of clinical factors and biological markers for overall survival. The median follow-up was 5.7 years (range, 2 months to 15.3 years). The results of the univariate analyses are shown in Table 1. As expected there was a significant association between the classical prognostic factors (tumor size, nodal status, distant metastases, grading, and ER) and outcome. No correlation was observed for menopausal and PR status.

**Expression of TβRI and TβRII in Breast Cancer Tissue and Adjacent Normal Tissue.** The tissue samples were classified into either positive or negative (not detectable) staining for TGF-β receptors. As far as possible normal tissue adjacent to the tumor tissue was analyzed as well. Expression of TβRI and TβRII was evaluated in 39 normal tissues. TβRI was detected in 54% of the normal tissue samples. In tumor tissue expression of TβRII was significantly more frequent. Of the tumor samples, 78% showed positive staining for the receptor (P = 0.0012). TβRII on the other hand was detected in the majority of the samples, and no significant differences between normal (64%) and tumor (72%) tissues were observed (Table 2).

Fig. 1 shows a representative immunohistochemical staining for TβRI and TβRII in tumor and adjacent normal tissue. The correlation of TβRII expression with tumor size, nodal status, distant metastases, histological grading, tumor stage, ER, PR, and menopausal
status of the patients was analyzed. The results are presented in Table 3.

TβRI showed a very strong correlation with tumor size and nodal status. The receptor was most frequently expressed in tumors >2 cm in diameter (pT1; P = 0.001) and in tumors of node-positive patients (P = 0.012). No correlations were observed with distant metastases, grading, hormone receptor, or menopausal status.

TβRII showed no significant correlations with any of the parameters analyzed.

Expression of the TGF-β Receptors and Overall Survival. Loss of TGF-β receptor expression has been associated with loss of TGF-β growth-inhibitory effects and progression to more aggressive tumor types (21, 25). However, these studies did not consider overall patient survival. To assess the influence of TGF-β receptor expression on prognosis of breast cancer patients Kaplan-Meier survival curves were calculated and log-rank analysis performed.

Surprisingly, patients with detectable expression of TβRII had significantly shorter overall survival times in comparison with patients with undetectable receptor expression (P = 0.0370; Fig. 2B). The mean overall survival time was 11.5 years [95% confidence interval (CI), 10.3–12.7] in patients without TβRII expression and 10.4 years (95% CI, 9.5–11.4) in patients with detectable expression of TβRII.

Similar results were obtained for TβRI. The effect of TβRI expression on the overall patient survival, however, was only nearly statistically significant (P = 0.0560; Fig. 2A) and probably due to the strong correlation of TβRI expression with tumor size and nodal status (Table 3).

ER Subgroup Analysis. To take hormonal influences into consideration the tissue specimen were additionally subgrouped into either ER positive or ER negative, and Kaplan-Meier survival curves were calculated.

Expression of TβRII defined a subset of patients in the ER-negative subgroup with strongly reduced overall survival times (P = 0.0083; Fig. 3B). The mean overall survival time was 11.3 years (95% CI, 10.2–12.4) for TβRII-negative patients.

Fig. 1 Immunohistochemical analysis of transforming growth factor-β receptor (TBR) I and TβRII expression in breast cancer tissue and adjacent normal tissue. Immunohistochemical staining was performed using polyclonal antibodies (TβRI, R-20; TβRII, C-16; both Santa Cruz Biotechnology) and a modified avidin-biotin-peroxidase complex technique. A, TβRI, normal breast tissue, staining intensity: 1, positive staining in 50% of cells, immunoreactive score (IRS): 2. B, TβRI, breast cancer tissue, staining intensity: 2, positive staining in 80% of cells, IRS: 6. C, TβRII, normal breast tissue, staining intensity: 1, positive staining in 50% of cells, IRS: 2. D, TβRII, breast cancer tissue, staining intensity: 3, positive staining in 80% of cells, IRS: 9. Specimens were counterstained with hematoxylin.
compared with only 8.3 years (95% CI, 6.8–9.7) for TβRII-positive patients. Additional stratification for treatment regimens (cyclophosphamide, methotrexate, and fluorouracil; and anthracyclin containing) gave similar results. In both treatment groups patients with detectable expression of TβRII had a considerably worse prognosis than patients without detectable expression of TβRII (data not shown).

In the ER-positive subgroup, on the other hand, expression of TβRII was without influence on the overall survival \( (P = 0.7035; \text{Fig. 3A}) \). The mean overall survival time was 11.1 years (95% CI, 9.6–12.6) for TβRII-negative patients and 11.4 years (95% CI, 10.3–12.6) for TβRII-positive patients.

TβRI expression had no effect on overall survival after stratification for the ER status. In the ER-positive as well as in the ER-negative subgroup patients with detectable TβRI expression had shorter survival times but differences to TβRI-negative patients were not significant (data not shown).

**Multivariate Analysis.** A multivariate Cox proportional hazards regression analysis was carried out to establish if expression of TβRII was an independent prognostic marker in the subgroup of ER-negative patients. The model initially included all of the parameters that were predictive of overall survival in the univariate analysis of the entire study group as presented in Table 1 (tumor size, nodal status, distant metastases, and tumor grading). A forward stepwise procedure was adopted to obtain the final model of significant predictors for overall survival consisting of the factors distant metastases, nodal status, and expression of TβRII. Inclusion of tumor size or grading into this model did not improve the log partial likelihood significantly. In the subgroup of ER-negative patients expression of TβRII was strongly associated with poor outcome, with a hazard ratio of 6.8 (Table 4).

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**Fig. 2** Kaplan-Meier overall survival analysis for transforming growth factor-β receptor (TβR) I (A) or TβRII (B).

**Fig. 3** Kaplan-Meier overall survival analysis for transforming growth factor-β receptor (TβR) II after stratification for estrogen receptor (ER). A, ER-positive patients; B, ER-negative patients.
RI and T analyzed the expression of T/H9252RII in 246 human come. In this retrospective exploratory study we have therefore considered the influence of receptor expression on disease out-
TGF-
RII (26–transduction pathways have been implicated in TGF-
RII (8). Downstream of the receptors different signal
and T/H9252 TGF-
RII signaling effects. The hormonal influence on activation of the TGF-
RII system adds an additional layer of complexity. A central role in
on the TGF-
RI was expressed in most of the tumor tissues (78%; Table 1).

Thus far only a few studies have examined the role of the
TGF-
RII was not
detectable expression of T/H9252RII another possible explanation for
RII expression. In
RI expression was associ-
detected previously for pancreatic cancer in which enhanced ex-
expression of T/H9252RII was significantly correlated with reduced overall survival. In pancreatic cancer increased expression of T/H9252RII was associated with high expression of plasminogen activator inhibitor 1 and matrix metalloproteinase 9 indicating a dissociation between TGF-
RII signaling leading to growth inhibition and extracellular matrix production (31).

Because TGF-
RI signals are mediated by a heteromeric
and extracellular matrix production (31).

Table 1 Summary statistics on patients clinical data and results of univariate analysis of classical prognostic factors (n = 246)

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of patients</th>
<th>Years (mean)</th>
<th>95% confidence interval (for the mean)</th>
<th>P*</th>
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<td>12.4–14.5</td>
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<tr>
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<td>11.9–13.7</td>
<td>&lt;0.0001</td>
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<td>10.6–12.2</td>
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</tr>
<tr>
<td>not known</td>
<td>71</td>
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</table>

* Log-rank test.
* ER, estrogen receptor; PR, progesterone receptor.

DISCUSSION

The role of TGF-β in breast cancer progression is unclear. TGF-β can display both tumor-suppressive and tumor-promoting effects. The hormonal influence on activation of the TGF-β system adds an additional layer of complexity. A central role in TGF-β signal transduction is played by the TGF-β receptors. TGF-β signals are mediated by an activated complex of T/H9252RI and T/H9252RII (8). Downstream of the receptors different signal transduction pathways have been implicated in TGF-β signaling (26–30).

Thus far only a few studies have examined the role of the TGF-β receptors in breast cancer tissues; none of these studies considered the influence of receptor expression on disease outcome. In this retrospective exploratory study we have therefore analyzed the expression of T/H9252RI and T/H9252RII in 246 human breast cancer tissues and adjacent normal tissues, and evaluated their association with prognosis. To assess hormonal influences on the TGF-β system we additionally included the ER status of the tumors into the analysis.

It has been suggested previously that loss of T/H9252RII expression may contribute to breast cancer progression and may be associated with a more aggressive phenotype (21). Our data show only a slight loss of T/H9252RII expression with increasing tumor grade, which does not reach statistical significance. T/H9252RII was expressed in a large part of the normal (64%) as well as the tumor tissue (72%; Table 2). The number of tumors with detectable expression of T/H9252RII decreased only slightly with high tumor grading (G1 + G2 75%, G3 64%). T/H9252RII was not correlated with any of the clinical parameters analyzed, including tumor size, node status, distant metastasis, grading, ER, PR, and menopausal status (Table 3). However, expression of T/H9252RII had a strong negative influence on prognosis. Patients with
detectable expression of T/H9252RII had significantly decreased survival times (P = 0.0370; Fig. 2B). These data indicate that in breast cancer, loss of TGF-β growth-inhibitory effects is not caused by loss of T/H9252RII expression. Similar results were obtained previously for pancreatic cancer in which enhanced expression of T/H9252RII was significantly correlated with reduced overall survival. In pancreatic cancer increased expression of T/H9252RII was associated with high expression of plasminogen activator inhibitor 1 and matrix metalloproteinase 9 indicating a dissociation between TGF-β signals leading to growth inhibition and extracellular matrix production (31).

Because TGF-β signals are mediated by a heteromeric complex of T/H9252RI and T/H9252RII another possible explanation for the absence of TGF-β growth-inhibitory effects and tumor progression in breast cancer could be a loss of T/H9252RII expression. In colon and prostate cancer loss of T/H9252RI expression was associated with increased malignant potential (25, 32, 33). No comparable studies exist for breast cancer. In our patient collective, T/H9252RI was expressed in most of the tumor tissues (78%; Table 1), and expression was more often detected in tumors of lower
table

<table>
<thead>
<tr>
<th>T/H9252RI</th>
<th>T/H9252RII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Tumor</td>
</tr>
<tr>
<td>Normal</td>
<td>18 (46)</td>
</tr>
<tr>
<td>Tumor</td>
<td>21 (54)</td>
</tr>
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</table>

P* = 0.0012

* χ2 test.
grade (81%; Table 3). Furthermore, expression of TβRI had a weak negative effect on prognosis. However, this correlation with survival is probably because TβRI expression was significantly more often detected in larger and node-positive tumors (1). Expression of TβRII had a weak negative effect on prognosis. However, this correlation with survival is probably because TβRII expression was significantly more often detected in larger and node-positive tumors (1). However, this correlation with survival is probably because TβRII expression was significantly more often detected in larger and node-positive tumors (1).

In summary our results suggest that loss of TGF-β growth-inhibitory effects in breast cancer cannot be attributed to either loss of TβRI or TβRII expression.

It has already been shown that a cross-talk between growth factors and steroid hormone receptors may be relevant to the regulation of growth and differentiation processes in hormone-dependent breast cancer. Thus far the only mutation in TβRI has been found in breast cancer metastases, but this mutation does not seem to occur frequently (37). Four inactivating mutations in TβRII have been found recently in recurrent breast tumors, but no TβRII mutations have been detected in primary breast cancers (38). In addition, an immunohistochemical study on the expression of Smad2, phosphorylated Smad2, and Smad4 suggests, that the majority of invasive breast carcinomas are able to actively mediate TGF-β signals (17).

The present study indicates that the ER status of a tumor is an important marker for the transition of TGF-β from tumor suppressor to tumor promoter. In ER-negative tumors expression of TβRII was associated with a subset of tumors that seemed to be highly aggressive leading to strongly reduced overall survival times (8.3 years; Fig. 3B). Simultaneous loss of both ER and TβRII, on the other hand, was associated with longer overall survival times (11.3 years) comparable with those of ER-positive patients and without TβRII expression (11.4 years and 11.1 years, respectively). Expression of TβRII proved to be an independent prognostic marker in the subgroup of ER-negative patients (Table 4).

Differences in treatment appear not to influence the impact of TβRII expression on overall survival in ER-negative patients. We distinguished between the two most commonly used treatment regimens, namely cyclophosphamide, methotrexate, and fluorouracil, and anthracycline-containing regimens. In each treatment group prognosis was worse for patients with detectable expression of TβRII.

It has already been shown that a cross-talk between growth factors and steroid hormone receptors may be relevant to the regulation of growth and differentiation processes in hormone

<table>
<thead>
<tr>
<th>TβRI</th>
<th>Negative</th>
<th>Positive</th>
<th>( P^a )</th>
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<th>Negative</th>
<th>Positive</th>
<th>( P^a )</th>
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<td>13 (27)</td>
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<td>post</td>
<td>32 (25)</td>
<td>95 (75)</td>
<td>0.069</td>
<td>33 (26)</td>
<td>94 (74)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \chi^2 \) test or Fisher’s exact test.

\( ^b \) ER, estrogen receptor; PR, progesterone receptor.
responsive tissues: the effect of epidermal growth factor seems to be partially mediated through the ER even in the absence of estradiol (39, 40). A similar cross-talk appears to exist for TGF-β signaling and the ER. The transcriptional activity of Smad3 can be suppressed by ER, whereas ER-mediated transcriptional activity can be increased by activation of TGF-β signaling (41).

In ER-positive tumors, TGF-β seems to act in an autocrine inhibitory fashion because a rapid increase in TGF-β2 levels under treatment with tamoxifen was correlated previously with clinical remission in patients with metastatic breast cancer (6). Loss of ER could evoke distinct changes in the cellular response to TGF-β and represent the starting point for a loss of TGF-β growth-inhibitory effects.

Therefore, a therapeutic approach that inhibits TGF-β signal transduction might turn out to be specifically effective for ER-negative patients with detectable expression of TβRII. A soluble TGF-β receptor type II protein that interferes with TGF-β binding to endogenous TGF-β receptors has been shown previously to reduce tumor cell motility, intravasation, and distant metastasis in a mouse model (34). In conclusion, our study TβRII proved to be an independent prognostic marker in the subgroup of ER-negative patients. According to the criteria of the American Society of Clinical Oncology (1) this study can be classified as evidence level III. Our results support a mechanism for breast cancer progression in which a selective loss of the growth-inhibitory action of TGF-β takes place, whereas tumor-promoting aspects of TGF-β signaling remain intact. We identified the ER as an important marker for changes in the tumor response to TGF-β. The precise interactions between ER and TGF-β signaling on the molecular level remain to be clarified. However, analysis of TβRII expression in ER-negative patients could be relevant for treatment decisions, as patients without detectable expression of TβRII had a prognosis similar to that of ER-positive patients.

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Prognostic Significance of Transforming Growth Factor β Receptor II in Estrogen Receptor-Negative Breast Cancer Patients

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