Global Characterization of the SRC-1 Transcriptome Identifies ADAM22 as an ER-Independent Mediator of Endocrine-Resistant Breast Cancer

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Abstract

The development of breast cancer resistance to endocrine therapy results from an increase in cellular plasticity that permits the emergence of a hormone-independent tumor. The steroid coactivator protein SRC-1, through interactions with developmental proteins and other nonsteroidal transcription factors, drives this tumor adaptability. In this discovery study, we identified ADAM22, a non-protease member of the ADAM family of disintegrins, as a direct estrogen receptor (ER)-independent target of SRC-1. We confirmed SRC-1 as a regulator of ADAM22 by molecular, cellular, and in vivo studies. ADAM22 functioned in cellular migration and differentiation, and its levels were increased in endocrine resistant-tumors compared with endocrine-sensitive tumors in mouse xenograft models of human breast cancer. Clinically, ADAM22 was found to serve as an independent predictor of poor disease-free survival. Taken together, our findings suggest that SRC-1 switches steroid-responsive tumors to a steroid-resistant state in which the SRC-1 target gene ADAM22 has a critical role, suggesting this molecule as a prognostic and therapeutic drug target that could help improve the treatment of endocrine-resistant breast cancer. Cancer Res; 72(1); 220–9. ©2011 AACR.

Introduction

Endocrine therapies such as tamoxifen are the treatment of choice for estrogen receptor (ER)-positive tumors and, although most patients initially respond to treatment, many eventually relapse. At a molecular and cellular level, increased tumor plasticity occurs in endocrine-resistant breast cancer in comparison with endocrine-sensitive tumors (1). Alterations in steroid receptor profile observed in clinical studies between primary and metastatic breast cancer, in particular with loss of progesterone receptor status, support the phenomenon of tumor adaptability in endocrine-resistant patients (2). These alterations are marked by increased signaling through growth factor networks and are driven, at least in part, through cross-talk between steroid and developmental pathways (3).

SRC-1 is central to the development of the endocrine-resistant phenotype and is an independent predictor of disease-free survival in tamoxifen-treated patients (4). As a coactivator protein, SRC-1 does not directly interact with the DNA but rather partners with other transcription factors to regulate gene expression. Relative to endocrine-sensitive tumors, increased SRC-1–ER-α interactions are observed in patients who are resistant to treatment (4). As the tumor progresses, however, increasing evidence suggests that SRC-1 engages in transcriptional interactions independently of ER.

Although initially described as a nuclear receptor coactivator protein, SRC-1 has been shown to interact with transcription factors running downstream of an activated mitogen—activated protein kinase pathway (5). These transcription factor interactions may represent one of the consequences of increased growth factor pathway signaling described in endocrine resistance. Work from this group and others has reported functional interactions between SRC-1 and the Ets family of transcription factors, Ets-2 and PEA3, and that this relationship is important in tumor progression and the development of metastasis (6–9). This occurs in part through SRC-1–mediated TWIST-suppressing luminal markers such as E-cadherin and β-catenin during epithelial–mesenchymal transition (7).

Using discovery tools, we investigated the signaling network central to SRC-1–mediated endocrine resistance. We identified a new ER-independent target of SRC-1, ADAM22. This disintegrin plays a role in endocrine-related tumor metastasis and opens up new possibilities as a therapeutic target.
Materials and Methods

Cell culture and treatments

Endocrine-sensitive MCF7, metastatic MDA-MB-231, and endocrine-insensitive SKBR3 were obtained from American Type Culture Collection and endocrine-resistant LY2 cells were a kind gift from R. Clarke, Georgetown, DC (10). Cells were grown as previously described (3). Letrozole-resistant cells (LeTr) were created by long-term treatment of overexpressing aromatase MCF7 cells to letrozole (Novartis) as previously described (3). Cells were maintained in steroid-depleted medium for 72 hours before treatment with hormones [estradiol (E2), 10^-8 mol/L; 4-hydroxytamoxifen (+OHT), 10^-7 mol/L; Sigma-Aldrich] over varying time periods. Primary cell cultures derived from patient tumors were cultured for 72 hours prior to experiments as described (3). All cell lines were tested (Source Biosciences, Life Sciences) for authenticity in accordance with American Type Culture Collection guidelines.

ChIP-sequencing and microarray analysis

To identify SRC-1 target genes, chromatin immunoprecipitation (ChIP)-seq was conducted in endocrine-resistant LY2 cells that were treated with vehicle or tamoxifen (+OHT) for 45 minutes and immunoprecipitated with anti-SRC-1 (sc-8995; Santa Cruz) antibody. To estimate the background, an input control, was included. Sequencing (35 base read length) was carried out by Illumina using the Illumina Genome Analyzer system as described previously, with technical replicates (3). ChIP-seq results are based on the analysis of a single sample, without biologic replicates. To identify functionally relevant SRC-1 target genes, mRNA was hybridized to whole genome microarray data was conducted using the BioConductor (version 2.4) suite of R packages (13). Briefly, data were preprocessed using germa (14) and an evident batch effect was removed with the ComBat approach (15). Differential expression was assessed using linear modeling and variance shrinkage through the empirical Bayes framework implemented in the LIMMA package (16). After correction for multiple hypothesis testing (17), probe sets with an adjusted value of P < 0.05 were selected as differentially expressed. To identify genes containing an SRC-1 peak in the promoter and also displaying differential expression in response to SRC-1 status, promoters were defined as 5 kbp of sequence upstream of RefSeq genes and found those which contained an SRC-1 peak. We selected the probe sets which were downregulated in the siSRC-1 samples, in both the presence and the absence of 4-OHT. Affymetrix probe set ID’s were mapped to RefSeq genes, and the intersection of these sets was determined.

siRNA and plasmids

Predesigned siRNAs directed against SRC-1 (Ambion AM16706;13631), AIB1 (Ambion AM 16706;116736), MYB (Ambion AM 4392420;59110), ADAM22 (Ambion 4390824; S28739), ER-α (Ambion, 4392421;S4824), and a nontargeting siRNA (Ambion, AM4635) were used to knockdown gene expression. The pcDNA3.1 plasmid containing full-length SRC-1 was used for overexpression studies and empty pcDNA3.1 was used as a control plasmid.

Knockout mouse studies

Knockout (KO) and wild-type (WT) mammary tumor cell lines were developed from primary tumors in SRC-1^-/-/PyMT and WT/PyMT mice as described in the work of Qin and colleagues (7).

qPCR

The mRNA levels of ADAM22 and SRC-1 were measured by qPCR. RNA was extracted from 3 wild-type cell lines (WT1, WT2, and WT3) derived from mammary tumors of WT/PyMT mice and 3 independent knockout cell lines KO1, KO2, and KO3 derived from mammary tumors of SRC-1^-/-/PyMT mice. The cDNA was prepared from 1 μg of RNA, and qPCR was carried out using matched universal TaqMan probes and gene-specific primers (Roche). Results are expressed as mean ± SD, n = 3.

Immunoblotting and communoprecipitation

Immunoblotting for MYB, SRC-1, and ADAM22 was carried out using rabbit anti-MYB (sc-517; Santa Cruz), anti-SRC-1 (sc-8995; Santa Cruz), and mouse anti-ADAM22 (H00053616-B01; MaxPab), respectively. Protein was immunoprecipitated with rabbit anti-SRC-1 (sc-8995; Santa Cruz) and subsequently blotted with anti-MYB.

ChIP studies

ChIP was carried out to confirm SRC-1, MYB, and ER-α recruitment to the ADAM22 promoter in either endocrine-resistant LY2 or endocrine-sensitive MCF7 cells as previously described (3). PCR was subsequently carried out with primers corresponding to the ADAM22 promoter (forward GGACCTCACAGTCACGGAGGT, reverse TCAGTGCTGCATTGTGCTTC).

Three-dimensional cultures

MCF7, LY2, and LetR cells were transfected with either siADAM22 or scrambled nontargeting siRNA. Twenty-four hours posttransfection, cells were harvested, 6 × 10^5 cells from each cell line were mixed in 400 μL of medium and 2% Matrigel (BD Biosciences) and subsequently seeded onto Matrigel matrix in 8-well chamber slides (BD Biosciences) and cultured...
for 14 days at 37°C/5% CO2. Cells were fixed in 4% paraformaldehyde and permeabilized with PBS containing 0.5% Triton X-100 for 10 minutes at 4°C. Cells were blocked in 10% goat serum (DAKO) and 1% bovine serum albumin. Cells were stained with Phallolidin 594 (Molecular Probes) for 20 minutes at room temperature and 4',6-diamidino-2-phenylindole (DAPI) for 5 minutes at room temperature. Slides were mounted (DAKO) and examined by confocal microscopy.

Migration assay
Migration assays were carried out as previously described (7).

Xenograft studies
Following ethical approval, 8-week-old female BALB/c SCID mice (Harlan) were implanted with 17-B-estradiol pellets from Innovative Research of America (0.25 mg/pellet, 60-day release). One week later, 5 x 10^6 MCF7 or LY-2 cells mixed with 50% Matrigel (BD biosciences) were implanted by intra-dermal injection on the rear dorsum. When the tumors reached 100 mm^3, the mice were randomly assigned to either treatment with 50% Matrigel (BD biosciences) were implanted by intra-dermal injection on the rear dorsum. When the tumors reached 100 mm^3, the mice were randomly assigned to either treatment (tamoxifen 5 mg/pellet, 60-day release) or control group (placebo pellet). Tumors were measured weekly until they had quadrupled in size at which point the animals were culled and tumors were stored in RNA later for subsequent Western blot analysis. Statistical analysis was conducted by calculating the growth rate of each individual tumor and treatment condition and analyzing them using an unpaired Student t test.

Tissue microarray/statistics
Patient breast tumor samples were collected the tissue microarray (TMA) constructed and data recorded as previously described (18). TMA was immunostained using mouse anti-ADAM22. Associations of ADAM22 with clinicopathologic variables and SRC-1 were examined using Fisher exact test. Kaplan–Meier graphs were used as an estimate of disease-free survival. Statistical analyses were conducted using Minitab. Cox’s proportional hazard model, using the Breslow method for ties. Survival times between groups were compared using the Wilcoxon test adjusted for censored values.

Accession codes
All ChIP-seq and expression array data are available from the Gene Expression Omnibus (GEO) database under series entry codes GSE28987 and GSE28645, respectively.

Results

Characterization of SRC-1 target genes in endocrine-resistant breast cancer
To address how SRC-1 mediates tumor adaptability and disease progression, we mapped SRC-1 transcriptional effects in endocrine-resistant breast cancer. To this end, we combined ChIP-seq/expression array analysis, molecular, cellular, and translational studies to define new SRC-1 targets central to the resistant phenotype. SRC-1-ChIP sequencing was conducted in endocrine-resistant (LY2) cells. Treatment with 4-hydroxytamoxifen significantly increased the number of ChIP-enriched intervals identified (Fig. 1A). About 41% of peaks in the 4-OHT–treated sample were close to the transcriptional start site, in the promoter, first exon, or upstream of the promoter (Fig. 1B). Furthermore, a significant SRC-1-ChIP enrichment was observed at the transcriptional start site in comparison with the transcriptional termination site (Fig. 1C). As a defined ER coactivator, an overlap between ER-binding sites and those identified for SRC-1 would be expected. In support of this, 4-OHT induced SRC-1 recruitment to the classic ER target genes, pS2, XBP1, and GREB1 in the endocrine-resistant cells (Supplementary Fig. S1A). Recently, examining SRC-3 ChIP DNA, Lanz and colleagues reported that 28% of SRC-3 peaks (FDR < 1) in estrogen-treated MCF7 cells have their sequence centers within 1 kbp of ER-binding sites (19). Here, using a modified version of the p53 scan (20), we found 43% of high confidence SRC-1 peaks (FDR < 1) in 4-OHT–treated LY2 cells, contained an ERE-binding motif within the peak (Fig. 1D). Though this analysis is restricted to ERE motifs rather than total ER binding, it raises the possibility that, in endocrine resistance, SRC-1 can interact with transcription factors to drive transcription, independently of ER.

We carried out microarray experiments on LY2 cells transiently transfected with scrambled siRNA or SRC-1 siRNA, untreated or treated with 4-OHT (Supplementary Fig. S1B) to assess SRC-1–dependent gene expression. Combining the ChIP-seq and expression array data sets, a total of 2,065 genes were significantly downregulated (P < 0.05) following SRC-1 knockdown and harbored a high confidence SRC-1 peak in the promoter region (Fig. 1E). We analyzed this list for novel metastatic oncogenes that represent potential druggable targets. The metalloproteinase ADAM22 was selected for functional validation through a series of molecular, in vivo, and translational studies. Interestingly, enrichment of SRC-1 at the ADAM22 promoter was observed in the LY2 cells on treatment with 4-OHT (Fig. 1F). Recruitment of SRC-1 to the ADAM22 promoter was confirmed using standard ChIP analysis (Fig. 1G).

SRC-1 regulates ADAM22 in endocrine-resistant breast cancer
We hypothesized that ADAM22 may be an effector of SRC-1–mediated endocrine-resistant disease progression. Knockdown of SRC-1 in LY2 cells reduced ADAM22 protein expression and conversely, forced expression of SRC-1 in the sensitive MCF7 cells increased ADAM22 expression (Fig. 2A). Knockdown of the p160, AIB1 had minor effects on ADAM22 expression in endocrine-resistant cells (Fig. 2A). In primary breast tumors, a significant association between transcript levels of SRC-1 and ADAM22 was observed (Fig. 2B). Furthermore, cells derived from mammary tumors of the SRC-1+/−/PyMT mouse lacked ADAM22 transcript, whereas high expression was evident in the wild-type PyMT mouse (Fig. 2C). Having established a role for SRC-1 in the regulation of ADAM22 in breast cancer, we addressed the question of whether or not this is ER dependent.
From bioinformatic studies, no ERE was observed in the promoter region of ADAM22. In endocrine-resistant LY2 cells, analyzing a 290-bp fragment of the ADAM22 promoter encompassing the SRC-1 peak, no recruitment of ER was observed, in the presence of either estrogen or 4-OHT (Fig. 2D). Moreover, knockdown of ER in LY2 cells did not alter ADAM22 expression (Fig. 2E). Further analysis of the promoter revealed a binding motif for the transcription factor MYB close to the SRC-1 peak (Fig. 2F). MYB expression has been reported in 64% of primary breast cancers and is associated with ER-positive tumors. Coimmunoprecipitation established that 4-OHT could drive MYB–SRC-1 interactions in endocrine-resistant tumors (Fig. 2G). ChIP analysis indicated that neither SRC-1 nor MYB are recruited to the ADAM22 promoter in the endocrine-sensitive MCF7 cells. In endocrine-resistant cells however, both SRC-1 and MYB were recruited to the promoter in the presence of estrogen and in particular 4-OHT (Fig. 2H). These findings support the hypothesis that as disease progression occurs in...
endocrine-resistant breast cancer, cellular adaptability can enable SRC-1 to regulate genes independently of ER.

ADAM22 promotes tumor progression in endocrine-resistant breast cancer

ADAM22 has a defined role as a postsynaptic neuroreceptor, but recent work examining its structure intimates a possible role for the protein in cell adhesion, spreading, and migration (21–23). These processes are critical to the metastatic phenotype, so we explored the role of ADAM22 in cell migration in endocrine-resistant breast cancer. We profiled a range of endocrine-sensitive, -insensitive, and -resistant cells along with metastatic breast cancer cells for expression of SRC-1 and ADAM22 (Supplementary Fig. S2). Low levels of
both ADAM22 and SRC-1 were found in the endocrine-sensitive and -insensitive cells, whereas stronger expression of both was found in the endocrine-resistant and metastatic cells. Furthermore, a marked increase in cell migration and de-differentiation was observed in both the 4-OHT-resistant LY2 and the letrozole-resistant LetR cells (Fig. 3A and B). Although MYB alone did not affect cell migration (Supplementary Fig. S3A), knockdown of ADAM22 with siRNA significantly reduced cell migration and restored differentiation in the endocrine-resistant cells (Fig. 3A and B;
Supplementary Fig. S3B) and in the ER-negative MDA-MB-231 (Supplementary Fig. S3C). Moreover, ADAM22 knockdown reverses the promigratory effects of 4-OHT observed in the endocrine-resistant cells (Fig. 3C). In addition, in xenograft studies, expression of ADAM22 was absent from both the 4-OHT–treated and untreated sensitive tumors and from the untreated resistant tumors. Treatment with 4-OHT, however, not only increased tumor volume in the resistant tumors but also induced ADAM22 expression (Fig. 3D and E). The neuronal protein, LGI1 serves as a specific extracellular ligand for ADAM22 (24). We found that treatment with recombinant LGI1 reduced cellular migration in endocrine-resistant cells in a similar manner to that observed with knockdown of ADAM22 (Fig. 3F). These data raise the distinct possibility of ADAM22 as a viable drug target for the treatment of endocrine-resistant breast cancer.

ADAM22 predicts poor disease-free survival in breast cancer patients

Previous molecular, in vivo, and clinical studies from this group and others have established SRC-1 as a key mediator of disease recurrence in endocrine-treated breast cancer (4, 8, 9). To determine the significance of the putative SRC-1 target ADAM22 in mediating disease progression, we examined its expression levels in a large cohort of patients with breast cancer and compared this with classical clinicopathologic parameters. ADAM22 was found to localize to the cell membrane of the tumor epithelial cells with strong cytoplasmic staining also being observed (Fig. 4A). In this cohort, expression of ADAM22 was found to significantly associate with SRC-1 (P = 0.002) and also with disease recurrence (P < 0.001; Table 1). In line with our bioinformatic, molecular, and in vivo studies, no association between

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**Table 1.** Associations of ADAM22 in TMA of patients with breast cancer with clinicopathologic variables and SRC-1 using Fisher exact test

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>ER%</th>
<th>HER2%</th>
<th>T stage 3/4</th>
<th>Nodal disease</th>
<th>High grade</th>
<th>Adjuvant Tx</th>
<th>SRC-1</th>
<th>Disease recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAM22+ (n = 198, 49%)</td>
<td>58.1 y</td>
<td>68%</td>
<td>22%</td>
<td>66%</td>
<td>51%</td>
<td>49%</td>
<td>36%</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td>ADAM22− (n = 210, 51%)</td>
<td>55.8 y</td>
<td>68%</td>
<td>18%</td>
<td>57%</td>
<td>51%</td>
<td>51%</td>
<td>40%</td>
<td>40%</td>
<td>29%</td>
</tr>
<tr>
<td>P</td>
<td>0.057</td>
<td>1.000</td>
<td>0.418</td>
<td>0.053</td>
<td>0.920</td>
<td>0.109</td>
<td>0.168</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All patients (n = 408)</td>
<td>56.1 y</td>
<td>68%</td>
<td>20%</td>
<td>61%</td>
<td>51%</td>
<td>45%</td>
<td>40%</td>
<td>34%</td>
<td>40%</td>
</tr>
</tbody>
</table>
ADAM22 expression and ER was observed (Table 1). Kaplan–Meier estimates of disease-free survival indicated that the absence of ADAM22 is a strong predictor of disease-free survival in breast cancer ($P < 0.0001$; Fig. 4B). Furthermore, in multivariate analysis using standard clinicopathologic parameters as well as SRC-1 and ADAM22, both SRC-1 and ADAM22 were found to be significant independent predictors of disease recurrence (ORs, 2.18 and 2.4, respectively; Table 2). These clinical ex vivo data firmly support our molecular observations that SRC-1 and its target ADAM22 can drive tumor progression in endocrine-resistant breast cancer (Fig. 5).

### Discussion

Endocrine tumors can adapt to overcome targeted therapy. There is now substantial evidence that the coactivator SRC-1 is central to this process. Though other members of the p160 family have been investigated in endocrine-related cancer, it is only SRC-1 that has been associated with the metastatic phenotype (7). SRC-1, a member of the p160 family of steroid coactivator proteins, is a master transcriptional regulator. SRC-1 was recently identified as the gene with the strongest selective pressure among ethnic populations analyzed by the International HapMap Project (25), illustrating the importance of the coactivator in human evolutionary adaptation. In this study, we use discovery tools to identify new SRC-1 target genes. Our intention was to uncover mechanisms of endocrine-related tumor metastasis and identify biomarkers and drug targets in this class.

ADAM22 was identified, and through a series of molecular and in vivo studies, confirmed as an SRC-1 target in endocrine-resistant breast cancer. ADAMs are multidomain transmembrane glycoproteins that have a diverse role in physiology and disease, with several members being targets for cancer therapy (21). Although most members of the ADAM family are active zinc metalloproteinases, 8 (including ADAM22) of 21 ADAMs lack functional metalloproteinase domains and are implicated in adhesion rather than membrane protein ectodomain shedding (26, 27). ADAM22 acts as a receptor on the surface of the postsynaptic neuron to regulate signal transmission, but a function for ADAM22 outside the nervous system has not been described to date (24).

Despite its well-documented role as an ER coactivator protein, evidence from ChIP-seq, bioinformatic, and molecular studies reported here suggest that SRC-1 can regulate ADAM22 independently of ER. A steroid receptor–independent role for SRC-1 is fast emerging. Interactions between SRC-1 and Ets family proteins have been implicated in tumor progression and the development of breast cancer metastasis (7–9). Furthermore, in the ER-negative PyMT SRC-1 knockout mouse model, although SRC-1 is not required for mammary tumor initiation, it is essential for the development of metastatic disease (28). Here, examination of the ADAM22 promoter revealed a binding motif for the transcription factor MYB. MYB is a proto-oncogene, though reports of its actions in breast cancer are limited, a role for MYB in steroid regulation has been suggested in several studies (reviewed in ref. 29). Although MYB alone had no significant effect on cell migration, results of our molecular experiments suggest that SRC-1 can regulate ADAM22, at least in part, through interaction with MYB, specifically in endocrine-resistant cells.

LGI1 acts as a specific extracellular ligand for the neurotransceptor ADAM22. It functions as a tumor suppressor of glioblastoma and neuroblastoma and has recently been shown to impair proliferation and survival in HeLa cells (30–32). Both LGI1 and ADAM22 are genetically linked to epilepsy, and the ligand/receptor complex has been suggested as a therapeutic target for synaptic disorders (24). Treatment of breast cancer cells resistant to either 4-OHT or letrozole, with recombinant LGI1, reduced cell migration. The antimigratory action of LGI1 observed here is consistent with the suppression of cell invasion observed in glioma cells (30). LGI1 may function by inhibiting the extracellular disintegrin domain of ADAM22. Furthermore, in a significant cohort of patients with breast cancer, ADAM22, along with SRC-1, was found to be an independent predictor of poor disease-free survival. Taken together, these studies provide strong evidence of ADAM22 as a mediator of metastasis and as a potential drug target for the treatment of endocrine-related metastatic disease.
SRC proteins are master regulators (33). SRC-1 through interactions with developmental proteins can increase cellular plasticity and enable tumors to adapt to endocrine therapy (3). Discovery studies described here have uncovered a steroid-independent SRC-1-mediated network in endocrine-resistant breast cancer, which has led to the identification of a new SRC-1 target, ADAM22. There is currently no effective treatment for patients with endocrine-related tumor metastasis. ADAM22 represents a rational new therapeutic target with a robust companion biomarker for the treatment of endocrine-resistant tumors.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interests were disclosed.

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