Signaling and Regulation

Matrix Metalloproteinase-1 Expression Can Be Upregulated through Mitogen-Activated Protein Kinase Pathway under the Influence of Human Epidermal Growth Factor Receptor 2 Synergized with Estrogen Receptor

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Abstract
In our previous work, Ets-1 upregulates human epidermal growth factor receptor 2 (HER2) induced matrix metalloproteinase 1 (MMP-1) expression. Based on the above knowledge and result, we hypothesized that estrogen receptor (ER) and its signaling pathway may affect MMP-1 expression under the influence of HER2. In addition, we investigated how the HER2 pathway cross-talk with the ER signaling pathway in genomic and nongenomic action of ER using reverse transcription-PCR, Western blot analysis, and ELISA assay. The results showed that ER-α expression increased MMP-1 expression under the presence of HER2. These upregulatory effects were mediated mainly by mitogen-activated protein kinase pathway and were reversed by downregulation of HER2 and/or ER. Activator protein DNA binding activity was involved in the MMP-1 expression. In summary, our results showed that ER can upregulate MMP-1 expression under the influence of HER2 in MCF-7 cells. In addition, this upregulatory effect was found to be mediated by mitogen-activated protein kinase pathway. MMP-1 might be an assigned target in interaction between ER and HER2. Mol Cancer Res; 8(7); 1037–47. ©2010 AACR.

Introduction
Approximately 70% to 75% of all breast cancers express the estrogen receptor (ER) and/or the progesterone receptor. Targeting the ER using antiestrogen agents to block ER activity and its signaling is the mainstay of the systemic hormonal treatment in the management of hormone receptor–positive breast cancers. Despite the clinical benefit of hormonal treatment in patients with hormone receptor–positive breast cancers, de novo and acquired resistance to endocrine therapy remains a significant clinical problem. Recent years have witnessed tremendous advances in the understanding of ER biology and revealed a complex process of ER signaling that includes interactions with other growth factor signaling pathways. Among them, cross-talk between ER and growth factor receptor pathways has important biological and therapeutic implications for the management of breast cancer (1–3). For the ER-positive, human epidermal growth factor receptor 2 (HER2)–overexpressing breast cancer, cross-talk between ER and growth factor receptor pathways has been known as main cause of hormonal resistance (4–8).

Estrogen signaling through ER occurs through several distinct pathways. In the “classic genomic pathway,” ligand-activated ER binds specifically to DNA at estrogen-responsive elements (ERE) through its DNA binding domain in the promoter region of the target genes, modulating the transcription of the genes. Estrogen also regulates gene expression by “a nonclassic genomic pathway” in which ER modulates the activity of other transcriptional factors such as activator protein (AP-1), NF-κB, or SP-1. Mitogen-activated protein kinase (MAPK)/PI3 pathways were reported to be involved with recruiting coactivators to the complex (9, 10). ER can also regulate cellular functions through nongenomic mechanisms called membrane-initiated steroid signaling. Membrane-associated ER increases the levels of second messengers such as c-AMP within minutes and activates various tyrosine kinase receptors such as epidermal growth factor receptor, HER2, and IGF-IR (3, 11, 12). Increased expression of EGFR and HER2 causes increased activation of EGF/HER2 heterodimers and increased phosphorylation of p42/44 MAPK, AKT, and nuclear ER. Therefore, enhanced growth factor signaling upregulates both the genomic and nongenomic activities of ER, resulting in resistance to endocrine therapy. However, the exact molecular mechanism has not fully elucidated how these growth factor signaling cross-talk with ER pathway. Moreover, the clinical significance of this cross-talk has not been accessed.

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In our previous work, cDNA microarray analysis to identify genes transcriptionally regulated by HER2 in MCF 7 breast cancer cells revealed that MMP 1 gene is one of the major target gene in HER2-overexpressing MCF-7 breast cancer cell line, and Ets-1 upregulates HER2-induced matrix metalloproteinase 1 (MMP-1) expression (13). Based on the above knowledge and result, we hypothesized that ER and its signaling pathway may affect HER2-induced MMP-1 expression. In addition, we investigated how the HER pathway cross-talks with ER signaling pathway in genomic and nongenomic action of ER, especially in the nucleus.

Moreover, there are some increasing evidence that ER regulates MMPs activities through AP-1 (14, 15). In addition, AP-1 transcriptional activity was reported to be enhanced by HER2 (16). However, whether the interaction between ER and HER2 can affect MMP-1 activity, and how it does, are need to be elucidated. Based on the above knowledge and result, we hypothesized that ER and its signaling pathway may affect HER2-induced MMP-1 expression. In addition, we investigated how the HER pathway cross-talks with ER signaling.

**Materials and Methods**

**Antibodies and reagents**

Anti-HER2, Anti-EGFR, Anti–ER-α, Anti–c-Jun, Anti–c-Fos, and Anti-JunD antibodies were purchased from Santa Cruz Biotechnology. Anti–phospho extracellular signal-regulated kinase (ERK) 1/2(Thr202/Thr204), Anti-ERK1/2, Anti-phospho Akt (Ser473), Anti-Akt, Anti-JunB, and Anti-FosB antibodies were purchased from Cell Signaling.

**FIGURE 1.** The effect of ER-α on HER2-induced MMP-1 expression. MCF-7/vector and MCF-7/HER2-14 cells were transfected with expression plasmids for ER-α for 24 h. A, total RNA was harvested. The mRNA expression levels of MMP-1 were analyzed using quantitative real-time RT-PCR. Columns, mean from three experiments; bars, SD, *** P < 0.0005 compared with the MCF-7/vector group; ##, P < 0.005 compared with the MCF-7/HER2-14 control group. B, total cell lysates were prepared and immunoblotted with HER2 and ER-α. β-Actin was used as a loading control. The conditioned medium was immunoblotted with MMP-1. C, the conditioned medium was subjected to ELISA to quantify secreted MMP-1. ***, P < 0.01 compared with the MCF-7/vector group; #, P < 0.05 compared with the MCF-7/HER2-14 control group.

**FIGURE 2.** Downregulation of ER-α inhibits HER2-induced MMP-1 expression. To knock down ER-α expression in MCF-7/HER2-14 cells, the cells were transfected with control siRNA oligo (NC) or ER-α siRNA oligo for 24 h. A, total RNA was harvested. The mRNA expression levels of MMP-1 were analyzed using quantitative real-time RT-PCR. Columns, mean from three experiments; bars, SD, *** P < 0.0005 compared with the MCF-7/vector group; #, P < 0.05 compared with the MCF-7/HER2-14 control group. B, total cell lysates were prepared and immunoblotted with HER2 and ER-α. β-Actin was used as a loading control. The conditioned medium was immunoblotted with MMP-1. C, the conditioned medium was subjected to ELISA to quantify secreted MMP-1. **, P < 0.01 compared with the MCF-7/vector group; #, P < 0.05 compared with the MCF-7/HER2-14 control group.
The Anti–β-Actin antibody was purchased from Sigma. The Anti–MMP-1 antibody was purchased from R&D Systems. Trastuzumab (Herceptin) was provided by Roche, Inc. Lapatinib (Tykerb) was provided by GlaxoSmithKline. Lapatinib (0.5 μmol/L) and lapatinib (0.2 μmol/L) were treated for 24 h. The mRNA expression levels of MMP-1 were analyzed using quantitative real-time RT-PCR. Columns, mean from three experiments; bars, SD. **, P < 0.001 compared with the MCF-7/vector group; ###, P < 0.005 compared with the MCF-7/HER2-14 control group.

B, MCF-7/HER2-14 cells were treated with lapatinib for 24 h. Cell lysates were prepared and immunoblotted with phospho-EGFR and phospho-HER2 as well as total EGFR and HER2. β-Actin was used as a loading control.

Quantitative real-time RT-PCR
Quantification of MMP-1 and glyceraldehyde-3-phosphate dehydrogenase cDNA was done using an ABI Prism 7900 Real-time PCR System (Applied Biosystems). All primers and probes (glyceraldehyde-3-phosphate dehydrogenase Cat # Hs99999905-m1; MMP-1 Cat # Hs00233958-m1) were obtained commercially and are proprietary; thus, sequences are not available (Taqman Gene Expression Assay, Applied Biosystems). Amplification was done under the following conditions: 50°C, 2 minutes; 95°C, 10 minutes; followed by 40 cycles of 94°C, 15 seconds and 60°C, 1 minute. Data were analyzed using the ABI Prism 7900 SDS 2.3 Software (Applied Biosystems).
cellular debris, and then decanted into a new conical tube. Conditioned media were stored at \(-80^\circ\)C until needed for experiments, at which time, the media were thawed and added directly to cells.

**Western blot analysis**

Whole-cell lysates were extracted with radioimmuno-precipitation assay buffer [0.5% sodium deoxycholate, 1% Nonidet P-40, 150 mmol/L NaCl, 50 mmol/L Tris (pH 7.5), 0.1% SDS, and 1 mmol/L phenylmethylsulfonyl fluoride]. Samples were placed on ice for 20 minutes with occasional vortexing. Protein concentrations were determined using a BCA-based protein assay kit (Pierce).

Equal amounts of samples were applied for SDS-PAGE under reducing conditions and were subsequently transferred to a nitrocellulose membrane. These membranes were incubated for 2 hours in a blocking solution containing 5% nonfat dry milk to inhibit nonspecific binding. The membranes were then incubated with the primary antibody for 2 hours. After several washes in PBS followed by incubation with horseradish peroxidase–conjugated secondary antibodies (Zymed), bound primary antibodies were detected with ECL chemiluminescent reagents (Amersham). To confirm equal protein loading within blots, stripping and reprobing with a \(\beta\)-actin antibody was done.

**FIGURE 4.** The effect of MAPK/AKT transduction pathway inhibitors on HER2-induced MMP-1 expression. MCF-7/HER2-14 cells were treated with U0126 (U; 10 \(\mu\)mol/L) or LY294002 (LY; 20 \(\mu\)mol/L) for 24 h. A, cell lysates were prepared and analyzed by immunoblotting with phosphorylated ERK1/2 and Akt as well as total ERK and Akt. The conditioned medium was immunoblotted with MMP-1. B, the mRNA expression levels of MMP-1 were analyzed using quantitative real-time RT-PCR. Columns, mean from three experiments; bars, SD. \(**\), \(P < 0.005\) compared with the MCF-7/vector group; \(##\), \(P < 0.005\) compared with the MCF-7/HER2-14 control group. C, MCF-7 cells were cotransfected with MMP-1 promoter-reporter construct together with empty expression vector or with expression plasmid for HER2. The cells were maintained for 18 h, cells were treated with U0126 or LY294002 for 24 h. Cells were harvested, and luciferase activity was measured. Columns, mean from three experiments; bars, SD. \(**\), \(P < 0.005\) compared with the MCF-7/HER2-14 control group. D, MCF-7/HER2-14 cells were treated with U0126 or LY294002 for 24 h. The conditioned medium was subjected to ELISA to quantify secreted MMP-1. Columns, mean from three experiments. \(**\), \(P < 0.005\) compared with the MCF-7/vector group; \(#\), \(P < 0.05\) compared with the MCF-7/HER2-14 control group; \(##\), \(P < 0.005\) compared with the MCF-7/HER2-14 control group.
ELISA for secreted MMP-1

Secreted MMP-1 from MCF-7 cells was quantified using the Human Pro–MMP-1 ELISA kit (R&D Systems), according to the protocol provided by the manufacturer. The absorbance at 450 nm was measured with a spectrophotometric plate reader.

Preparation of promoter-reporter constructs

A promoter fragment of the human MMP-1 gene, from −4334 to +5218 relative to the transcription start point, was amplified from human DNA by PCR, using a pair of primers (5′-agatgtaagagctgggaaaggacgg-3′/5′-tcagtgcaaggtaagtgatggcttc-3′) and Accuprime Pfx DNA polymerase (Invitrogen). The fragment was subcloned into the pCR-XL-TOPO vector (Invitrogen) for propagation in bacteria. The isolated plasmid was digested with the restriction enzymes MluI and XhoI to release the inserted fragment. The fragment was resubcloned in the sense orientation into the promoter-free pGL3-Basic vector (Promega) at the MluI and XhoI sites in the 5′ flanking region of the luciferase sequence.

Luciferase assays

MCF-7 cells were transiently transfected with the reporter constructs using Effectene Transfection Reagent. After transfection, whole-cell lysates were prepared and luciferase activity was measured using a luciferase activity assay kit (Promega).

Electrophoretic mobility shift assays

The following double-stranded oligonucleotides were used in the study: AP-1 binding sites in the human MMP-1 promoter region, 5′-TAA TCA AGA GGA TGT TAT AAA GCA TGA GTC AGA CA-3′ (17); mutant AP-1 binding sites in the human MMP-1 promoter region, 5′-TAA TCA AGA GGA TGT TAT AAA GCA TGA GTT GGA CA-3′; AP-1, 5′-CGC TTG ATG ACT CAG CCG GAA-3′ (Santa Cruz Biotechnology); mutant AP-1, 5′-CGC TTG ATG ACT TGG CCG GAA-3′ (Santa Cruz Biotechnology); ERE, 5′-GGA TCT AGG TCA CTG TGA CCC CCG ATC-3′ (Santa Cruz Biotechnology); and mutant ERE, 5′-GGA TCT AGT ACA CTG TGA CCC CCG ATC-3′ (Santa Cruz Biotechnology). The probe was purified and labeled with [γ-32P] ATP using T4 polynucleotide kinase. Labeled oligonucleotides (10,000 cpm), 10 μg of nuclear extract, and binding buffer [10 mmol/L Tris-HCl (pH 7.6), 500 mmol/L KCl, 10 mmol/L EDTA, 50% glycerol, 100 ng of poly (dl-dC), and 1 mmol/L DTT] were incubated for 30 minutes at room temperature in a final volume of 20 μL. The resulting reaction mixture was analyzed by electrophoresis on
a 5% polyacrylamide gel in a 0.5 x tris-borate/EDTA buffer. Specific binding was controlled by competition with a 50-fold excess of cold oligonucleotide. For purposes of the supershift/inhibition assay, 1 to 2 μg of a specific super-shifting antibody against AP-1 were incubated with the nuclear extract on ice for 1 hour before the addition of labeled oligonucleotide to the binding reaction.

Statistical analysis
The results are expressed as means ± SEM, and differences between means for two groups were determined by unpaired Student’s t test. The minimum significance level was set at P value of <0.05 for all analysis. All experiments were done at least thrice.

Results

The effect of ER-α on HER2-induced MMP-1 expression
To determine the effect of ER-α on HER2-induced MMP-1 expression, we conducted quantitative RT-PCR (Fig. 1A) and Western blotting for MMP1 (Fig. 1B), and ELISA (Fig. 1C) in MCF-7/vector and MCF-7/HER2 stable cell lines after transient transfection of ER-α. As shown in the Fig. 1A, transient transfection of ER-α in MCF-7 cell caused significant increase in MMP-1 expression compared with marked increase of MMP-1 expression induced by HER2 stable transfection in MCF7/HER2 cell line. To confirm these change, we conducted Western blot for MMP1 and ELISA (Fig. 1B and C). Western blot for MMP-1 and ELISA for MMP-1 expression showed that ER-α expression increased MMP-1 expression under the presence of HER2.

Downregulation of ER-α inhibits HER2-induced MMP-1 expression
Whether ER downregulation with small interfering RNA (siRNA)–specific for ER-α (siER-α) could suppress MMP-1 expression induced by HER2 overexpression, we performed quantitative RT-PCR, Western blotting, and ELISA for pro–MMP-1 (Fig. 2) after treatment with 20 nmol/L of ER-α siRNA in HER2-overexpressing MCF-7 stable cell (MCF-7/HER2-14). Downregulation of ER-α resulted in marked inhibition of MMP-1 expressions.

The effects of HER2-targeting agents on HER2-induced MMP-1 expression
HER2-induced MMP-1 expressions were inhibited by trastuzumab (anti-HER2 antibody) and lapatinib (EGFR and HER2 tyrosine kinase inhibitor; Fig. 3A). p-EGFR and p-HER2 expressions were markedly inhibited by
lapatinib in a dose-dependent manner (Fig. 3B). However, HER2 expression was markedly increased (Fig. 3B). β-Actin was used as a loading control.

**Effect of MAPK/AKT pathway inhibitors on HER2-induced MMP-1 expression**

To investigate the signaling pathway of MMP-1 expression in HER2-transfected stable MCF-7 cells, we used U0126, a specific inhibitor of the ERK/MAPK signal transduction pathway, and LY294002, specific inhibitors of the Akt signal pathway. First, MCF-7/HER2-14 cells were incubated for 24 hours after the addition of U0126 and LY294002. Likewise, MAPK and Akt expression were measured through mRNA expression levels of MMP-1 and HER2 as analyzed by Western blotting and RT-PCR (Fig. 4A-D). As shown in Fig. 4A, declines in p-MAPK expression and subsequent MMP-1 expression, which had been upregulated by HER2, were indeed observed in MCF-7/HER2-14 cells treated with U0126. However, there was no definite change in Akt expression after treatment of LY294002 in RT-PCR, although the Western blot results showed downregulation of pAKT. As shown in Fig. 4B to D, quantitative RT-PCR, luciferase assay, and ELISA assay for pro-MMP-1 showed marked decreased expressions of MMP-1 after treatment of U0126. However, there was no definite decline in p-Akt expression, and MMP-1 expressions were observed in MCF-7/HER2-14 cells treated with LY294002.

**HER2 upregulates an AP-1 DNA binding activity**

The transcription factor AP-1 regulates MMP-1 through its binding site on the MMP-1 promoter (17). To determine the effect of HER2 on AP-1 activation, which is most commonly involved in nonclassic ER genomic pathway, we tested MCF-7 cells that had been stably transfected with a HER2 expression vector. Fig. 5A and B showed that the DNA binding activities of AP-1 and MMP-1 AP-1 factors are increased only in wild-type AP-1 and MMP-1 AP-1 probes. DNA binding activities of mutant AP-1 and MMP-1 AP-1 were not increased. Nuclear samples were analyzed as illustrated in Fig. 5 using electrophoretic mobility shift assay (EMSA) and a 32P-labeled AP-1 oligonucleotide probe. As shown in Fig. 5C, the DNA binding activity of AP-1 factor in HER2-transfected cells was significantly increased in various MCF-7/HER2 clones. To determine whether HER2 activation results in the increased binding of the AP-1 recognition sequence in the MMP-1 promoter region, we compared the binding of nuclear proteins to the AP-1 binding site of the MMP-1 promoter between pcDNA3.1 and HER2-transfected MCF-7 cells. As shown in Fig. 5D, the DNA binding activities of AP-1 MMP-1 AP-1 site in various HER2 stable MCF-7 cells were significantly increased.

**Upregulated AP-1 DNA binding activity was reversed by the downregulation of HER2 and ER**

To investigate the inhibitory effect of trastuzumab, anti-HER2 monoclonal antibody, and siER on enhanced AP-1 DNA binding activity, EMSA was performed on AP-1 probe and labeled oligo containing AP-1 binding site in the human MMP-1 promoter. Increased AP-1 binding activity was dramatically decreased by trastuzumab and siER (Fig. 6A-D).
HER2-induced MMP-1 expression is mediated by JunB binding to the AP-1 site

To determine whether a specific AP-1 family member was involved in the process observed above, complexes between 32P-labeled AP-1 and MMP-1 AP-1 site oligomers and nuclear extracts from MCF-7 HER2-14 stable cell were incubated with various antibodies (c-Jun, c-Fos, JunB, and FosB) in a supershifted EMSA. Supershifts of the AP-1 binding and MMP-1 AP-1 site complexes (arrows) were detected with an anti-JunB antibody (Fig. 7A and B).

Effect of U0126 and LY294002 treatment on HER2-induced DNA binding activity

MCF-7/HER2-14 cells were treated with U0126, a MAPK inhibitor, or LY294002, an Akt inhibitor, for...
24 hours to investigate the involvement of the Akt/MAPK pathways in HER2-mediated activation of AP-1 using ELISA to evaluate AP-1 and AP-1 in MMP-1 promoter binding. As shown in Fig. 8, AP-1 activities were regulated by HER2 and were inhibited by U0126 MAPK inhibitor (A), but not by LY294002 (B).

**ER-dependent component of MMP induction and downstream signaling**

Quantitative RT-PCR showed increased mRNA expression levels of MMP-1 (Fig. 9A). EMSA showed protein binding in the AP-1 binding site in the human MMP-1 promoter and ERE (Fig. 9B). RT-PCR of ER downstream pathway showed decreased expressions of progesterone receptor, stromal cell–derived factor 1, and pS2.

**Discussion**

One of the main explanations for endocrine resistance in ER-positive breast cancer is cross-talk between ER and growth factors signaling pathways such as EGFR, HER2, IGF-IR (3, 18-20). Obviously, such hormone resistance has a specific meaning for patients with HER2-overexpressing breast cancers. Whereas ER positivity predicts efficacy of endocrine agents, preclinical and clinical data suggest that HER2-overexpression confer intrinsic resistance to hormonal treatment. Therefore, studies aimed at overcoming hormone resistance are necessary, particularly in the context of HER2-overexpressing breast cancers.

For the reasons described above, our study has several implications. First, MMP-1 has been suggested as one important target of HER2 signaling pathways, which was positively influenced by ER. We previously showed that HER2 induces MMP-1 expression, and Ets-1 enhances HER2-induced MMP-1 expression (13), inferring that MMP-1 might play a role in breast cancer by HER2. Furthermore, we now show that ERK/MAPK signaling pathway is responsible for HER2-induced MMP-1 upregulation, suggesting that the ER pathway was positively implicated in this pathway (Figs. 1-3 and 6 and 7). However, how ER could work in relation with MAPK needs to be defined.

Second, the results of the present study help to our understanding of cross-talk between ER and HER2 pathway. Our observations showed that this cross-talk increases the level of the MMP-1 associated with AP-1 through Akt/MAPK signaling pathways, and that this upregulation could be blocked by a MAPK-specific inhibitor, U0126. Importantly, our results implicate that the ERK/MAPK pathway may have more essential role than the Akt pathway in MMP-1 activity (Figs. 3 and 8). Otherwise, increasing effect of ERK caused by LY294002 (21) might not result in the downregulation of MMP-1 expression.

There is some additional evidence that ER can affect the transcription of genes in many functional categories, especially for patients with long-term exposure to tamoxifen (4, 22-25). Thus, although our findings reveal cross-talk between these pathways in the presence of HER2 and allow estrogen to upregulate MMP-1, they also imply that MMP-1 is under additional control of ER activation in the case of HER2-overexpressing ER-positive breast cancer cells.

MMP-1 inhibition strategies have failed in many clinical trials. Nevertheless, the need to validate the role of MMP-1s in cancer development and progression still remains (26-28). Interestingly, MMP-1 was reported as one of the first verified AP-1 target genes, and several other MMPs, including MMP3 and MMP9, have long been known to be regulated by AP-1 in a variety of cellular contexts (29, 30). Our results clearly showed that HER2 overexpression can increase the binding activity of AP-1 to the AP-1 site within the MMP-1 promoter. This binding could be reversed by the anti-HER2 monoclonal antibody trastuzumab; the finding of which implicated that increased AP-1 transcriptional activity is involved in HER2-induced MMP-1 expression. Subsequent functional studies using EMSA revealed that the AP-1 motif is a crucial part of the MMP-1 upregulatory
effect induced by HER2 in MCF-7 breast cancer cells. We also observed JunB involvement in AP-1 activation.

Considering the capacity of ER to regulate MMP-1 under the influence of HER2, MMP-1 might be an assigned target in interaction between ER and HER2. Interestingly, increased AP-1 and MMP-1 activities did not result in increased ER downstream pathway (Fig. 9). This finding reflects that “ER is working nongenomically.” Actually, there are some evidence that increased membrane ER activity results in the loss of progesterone receptor expression in relation with endocrine resistance (31). Furthermore, ER redistribution to the cytoplasm associated with HER2 interaction (32). There are some evidence that MMP-1 is associated with breast cancer metastases, especially to the bone (33-36). On the other hand, the bone is the most common metastatic site of breast cancer and is usually associated with better prognosis and dormant course than visceral metastases, especially in cases of bone-only metastases (37, 38). Taken together, MMP-1 is expected to be a possible candidate gene of ER regarding cross-talk between ER and HER2. Surely, this hypothesis is going to be validated with further translational research. In conclusion, this study infers that ER can upregulate MMP-1 expression under the influence of HER2, and the MAPK pathway was involved in this upregulation (Fig. 10). Furthermore, genomic and nongenomic ER pathways might be involved in this upregulation of ER in MMP-1 expression in the presence of HER2. The implication of MMP-1 as a potential target regulated by ER in HER2-overexpressing breast cancer should be validated in further translational research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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