Insulin-like Growth Factor Binding Proteins IGFBP3, IGFBP4, and IGFBP5 Predict Endocrine Responsiveness in Patients with Ovarian Cancer

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Abstract

Purpose: This study sought to explore the predictive value of the insulin-like growth factor (IGF) binding proteins (IGFBP) as markers of response in ovarian cancer patients treated with the aromatase inhibitor letrozole.

Experimental Design: IGFBP mRNA expression in cell lines was measured by quantitative reverse transcription-PCR and IGFBP protein expression measured in sections from primary tumors of patients treated with letrozole by semiquantitative immunohistochemistry.

Results: Quantitative reverse transcription-PCR analysis showed that IGFBP3 and IGFBP5 were down-regulated and IGFBP4 was up-regulated by 17β-estradiol (E2) in an estrogen receptor (ER)–positive ovarian cancer cell line. Expressions of IGFBP1, IGFBP2, and IGFBP6 were unaffected by E2. The E2 modulation of these genes was reversed by tamoxifen. Using ERα-specific (propyl pyrazole triol) and ERβ-specific (diarylpropionitrile) agonists, the gene expression modulations produced by E2 could be replicated by propyl pyrazole triol but not by diarylpropionitrile. For ovarian cancer patients being treated with letrozole, we tested the predictive value of the IGFBPs in paraffin-fixed sections from their primary tumors by semiquantitative immunohistochemistry. Using serum CA125 as an indicator of progression/response, significant differences in expression levels of IGFBPs were observed between tumors from CA125 responding/stable patients compared with tumors from progressing patients. Mean immunoscores for IGFBP3 and IGFBP5 were significantly lower, and mean expression of IGFBP4 was significantly higher in tumors from patients demonstrating CA125 response or stabilization compared with CA125 progression.

Conclusion: These results indicate that expression levels of certain IGFBP family members in ovarian cancers are estrogen regulated and can, thus, help identify patients who could benefit from endocrine therapy.

Epithelial ovarian cancer is the leading cause of death from gynecologic malignancies in the Western world, and new approaches are required to treat this disease. Ovarian cancers frequently express high levels of estrogen receptor α (ERs), which raises the possibility that ERs might represent a therapeutic target. We have previously shown that ERs-positive ovarian cancer cell line models are growth responsive to estrogen and antiestrogen manipulations both in vitro and in vivo (1–4). The antiestrogen tamoxifen has been widely used to treat chemoresistant diseases with inconclusive results (5, 6). More recently, we and others have shown that the aromatase inhibitor letrozole, which acts by depleting levels of estrogen available to ERs, has shown clinical benefit in a subgroup of ovarian cancer patients (7, 8). In a phase II trial of letrozole in patients with ovarian cancer, we showed that a response or stabilization of disease, as defined by CA125 levels, was associated with higher levels of ERs, low erbB2 receptor levels, and high epidermal growth factor receptor expression (7), and an extension to this trial has confirmed that expression of ERs predicts sensitivity (9). The overall combined rate of CA125 marker response and stabilization was 32% in the first trial, and the median survival was 14 months with 17% of patients alive at 2 years (7). In the follow-up study that was restricted to patients with moderate-to-high ERs-expressing cancers, the CA125 response rate increased to 16% with CA125 stabilization shown in a further 37% of patients (9).

To search for predictive markers to help identify estrogen-sensitive ovarian cancers, we used microarray analysis to highlight a panel of potentially useful gene markers (4). That study explored 17β-estradiol (E2) modulation of gene expression in an ERα-positive ovarian cancer cell line (PE01) in vitro.

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double-stranded DNA-binding dye SYBR Green. Primer sequences used for amplification was confirmed by product melt analyses. PCR primers for tamoxifen (Sigma), ERα, and ERβ were specified, cells were treated with E2 (Sigma, Poole, United Kingdom), or ERβ. Cells were blocked by incubating sections in 3% H2O2. Sections were immersed in citrate buffer (0.005 mol/L, pH 6.0) and microwaved for 3–5 min, except for IGFBP6 staining (because the antibody showed improved staining in the absence of microwaving). Slides were washed in 0.05 mol/L Tris-NaCl buffer (pH 7.6) and then incubated in 20% FCS for 10 min. Primary antibodies were added for 1 to 2 h. The following antibodies were used: IGFBP1 (Ab10732, Abcam, Cambridge, United Kingdom; 1:5 dilution), IGFBP2 (Ab4243, Abcam; 1:5 dilution), IGFBP3 (Ab4248, Abcam; 1:500 dilution), IGFBP4 (17661, USBiological, Swampscott, MA; 1:3 dilution), IGFBP6 (Ab4255, Abcam; 1:300 dilution), IGFBP6 (Ab4258, Abcam; 1:5 dilution). The anti-IGFBP1 antibody is noncross reactive with IGFBP2, IGFBP3, and IGFBP4. The anti-IGFBP3 antibody has minimal cross-reactivities with IGFBP1 (<10%), IGFBP2 (<0.2%), IGFBP3 (<0.1%), and IGFBP5 (0.5%). The anti-IGFBP4 antibody shows no cross-reactivities. The anti-IGFBP6 antibody has minimal cross-reactivities with IGFBP1 (<0.5%), IGFBP2 (<0.1%), IGFBP3 (<0.1%), and IGFBP4 (<0.5%). The cross-reactivities of the IGFBP2 and IGFBP6 antibodies are undefined.

After primary antibody incubation, sections were washed in Tris-NaCl buffer. A streptavidin-biotin multilink method (Stavrigen Multi-link kit, Biogenex, San Ramon, CA) was used for detection of reactivity. Sections were stained with secondary multilink antibody (1:20 dilution for 30 min), followed by horseradish peroxidase–labeled streptavidin complex (1:20 dilution for 30 min). Diaminobenzidine tetrachloride was used as chromogen and applied for 5 min. Slides were then lightly counterstained with hematoxylin and mounted conventionally. IGFBP expression was measured using a scoring system consisting of the product of the percentage of positive cells and intensity of staining (0–3), producing a histoscore ranging from 0 to 300. All tumor cells in the section were counted in the scoring system. Sections were scored by two independent readers, and mean values were obtained. Where initial scoring produced a value divergent by >10%, these sections were rescored until agreement was reached. Differences between groups were tested using the Mann-Whitney test and ANOVA, followed by a Dunnett’s multiple comparisons test and Fisher’s exact test where described.

Materials and Methods

Cell culture. The PEO4 and PE014 cell lines were developed at the Edinburgh Cancer Research Center (21). Cell lines were routinely cultured at 37°C, 90% humidity, and 5% CO2 in RPMI 1640 (Life Technologies, Paisley, United Kingdom) containing 10% heat-inactivated FCS, 100 μg/mL streptomycin, and 100 μg/mL penicillin. Where specified, cells were treated with E2 (Sigma, Poole, United Kingdom), tamoxifen (Sigma), EGR agonist (propyl pyrazole triol, Tocris, Avonmouth, United Kingdom), or ERβ-specific agonist (diarylpropionitrile, Tocris) at the concentrations shown.

Real-time quantitative PCR. Reverse transcription-PCR was done using a Rotorgene 2000 (Corbett Research, Cambridge, United Kingdom) and a one-step Quantitect reverse transcription-PCR kit (Qiagen, Cowley, United Kingdom) as per protocol. Thermal cycling conditions were 50°C for 30 min and 95°C for 15 min, followed by 45 cycles of 95°C for 15 s, 55°C for 30 s, and 72°C for 45 s. Single-product amplification was confirmed by product melt analyses. PCR primers were designed by Primer 3.0 and Blast searched to check specificity. Specific PCR amplification products were detected by the fluorescent double-stranded DNA-binding dye SYBR Green. Primer sequences used were as follows:

IGFBP1: GCTTACGCACAGGAGGAC and TATCTGGCAGTGGGGCCTC
IGFBP2: GAGAAGGTCATCAGGCGCA and GGGATGGCCAGGAGTACAG
IGFBP3: GCCGGAGACAGAATTATGTC and AGGCTGGCCATACCTATCCA
IGFBP4: GCCCAAGGACTGAGACTG and CACATGCACAAAATTCGAG
IGFBP5: AAGACGGTCAGGCCAAGTCCAG and GTAATCCGGGCTCTCCTGCT
IGFBP6: AAGATGTGACCCGCAAGAG and GTGTAAGGCTCCATGTTGCTA
ACTIN: CTACGTCGCCCAGTCCGACG and GATGGAGGCGGCCGATCACAGCC

IGFBPs and Endocrine Response in Ovarian Cancer

Immunohistochemistry. We had previously recruited a series of 60 ovarian cancer patients to receive letrozole (2.5 mg/d) daily at the time of CA125 relapse of their disease (7). Of these, CA125 data were evaluable for 49 patients at 12 weeks of treatment. At this time, five patients showed >50% reduction in their CA125 value (CA125 response) and 14 patients had CA125 reductions, which fell by <50% and then remained stable (i.e., did not increase to >50% of the initial CA125 value) at 12 weeks, whereas the CA125 values of 30 patients progressed by >50%. Formalin-fixed paraffin-embedded histologic sections from tumor specimens resected at the initial laparotomy were assessed for the presence of biochemical markers. Sections (3 μm) were deparaffinized and rehydrated. Endogenous peroxidase activity was blocked by incubating sections in 3% H2O2. Sections were immersed in citrate buffer (0.005 mol/L, pH 6.0) and microwaved for 3–5 min, except for IGFBP6 staining (because the antibody showed improved staining in the absence of microwaving). Slides were washed in 0.05 mol/L Tris-NaCl buffer (pH 7.6) and then incubated in 20% FCS for 10 min. Primary antibodies were added for 1 to 2 h. The following antibodies were used: IGFBP1 (Ab10732, Abcam, Cambridge, United Kingdom; 1:5 dilution), IGFBP2 (Ab4243, Abcam; 1:5 dilution), IGFBP3 (Ab4248, Abcam; 1:500 dilution), IGFBP4 (17661, USBiological, Swampscott, MA; 1:3 dilution), IGFBP5 (Ab4255, Abcam; 1:300 dilution), IGFBP6 (Ab4258, Abcam; 1:5 dilution). The anti-IGFBP1 antibody is noncross reactive with IGFBP2, IGFBP3, and IGFBP4. The anti-IGFBP3 antibody has minimal cross-reactivities with IGFBP1 (~10%), IGFBP2 (~0.2%), IGFBP3 (<0.1%), and IGFBP5 (0.5%). The anti-IGFBP4 antibody shows no cross-reactivities. The anti-IGFBP6 antibody has minimal cross-reactivities with IGFBP1 (~0.5%), IGFBP2 (~0.1%), IGFBP3 (~0.1%), and IGFBP4 (~0.5%). The cross-reactivities of the IGFBP2 and IGFBP6 antibodies are undefined.

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Results

IGFBP3, IGFBP4, and IGFBP5 are modulated by estrogen in an estrogen-responsive ovarian cancer cell line in vitro. The modulation by E2 of the individual IGFBP family members was first investigated in the ER-positive, estrogen growth–sensitive PE04 cell line. After exposure to 0.1 nmol/L E2 for 6 h, IGFBP3 and IGFBP5 expressions were down-regulated, whereas IGFBP4 was up-regulated and IGFBP1, IGFBP2, and IGFBP6 expressions...
were unchanged (Fig. 1). Tamoxifen alone had negligible effects on expression but was able to reverse the decreased expressions of IGFBP3 and IGFBP5. To assess whether these effects were likely to be mediated via ERα or ERβ, we compared the effects of a ERα-specific agonist (propyl pyrazole triol; ref. 22) and a ERβ-specific agonist (diarylpropionitrile; ref. 23) with E₂. The E₂-modulated changes were very similar to those produced by propyl pyrazole triol, whereas diarylpropionitrile had little effect, suggesting that ERα accounts for E₂ effects on IGFBP expression. Expression of all the six IGFBPs in the ERα-negative, estrogen growth–unresponsive PE014 cell line was unaffected by E₂ (data not shown).

**Expression of IGFBPs in primary ovarian cancers and association with letrozole clinical response.** The expression of individual IGFBP was measured by semiquantitative immunohistochemistry in paraffin-fixed sections obtained from ovarian cancers of patients treated in the initial phase II clinical trial of letrozole (7). In that study, two groups of patients had been identified: the first group showing either CA125 reduction or a minimal increase of <50% (CA125 nonprogressors) and the second group showing CA125 increase of ≥50% (CA125 progressors). Examples of staining are illustrated in Fig. 2. Immunoscore values for individual tumors were measured and are shown in Fig. 3. Mean values are recorded in Table 1.

![Graphs showing IGFBP expression](image-url)

IGFBP1 protein expression was detected in approximately half (53%, 22 of 42 tumors) of the ovarian cancers studied, whereas IGFBP2 was expressed in virtually all tumors (90%, 38 of 42 positive). The mean immunohistoscore was not significantly different between the CA125 nonprogressors and the CA125 progressors for either IGFBP1 (22 versus 26, respectively; \( P = 0.653; \) Mann-Whitney test) or IGFBP2 (92 versus 71, respectively; \( P = 0.212 \)). In contrast, the mean immunohistoscore for IGFBP3 was highly significantly different between the nonprogressors and progressors (60 versus 121, respectively; \( P < 0.0001 \)) with mean expression levels being lower in the CA125 nonprogressors group. IGFBP3 expression was detected in 40 (95%) of 42 tumors. Although IGFBP3 was reduced in nonprogressors relative to progressors, expression of IGFBP4 was increased (142 versus 50, respectively; \( P = 0.0017 \)). IGFBP4 expression was detected in 33 (72%) of 46 tumors, and IGFBP5 expression in 44 (100%) of 44 tumors. In a pattern similar to that of IGFBP3, the mean immunohistoscore of IGFBP5 was highly significantly different between the CA125 nonprogressors and the CA125 progressors (136 versus 204, respectively; \( P = 0.0019 \)), with the mean expression level being lower in the CA125 responsive group. IGFBP6 expression was detected in 38 (93%) of 41 tumors. As for IGFBP1 and IGFBP2, the mean immunohistoscore was not significantly
different between the CA125 nonprogressors and the CA125 progressors (75 versus 108, respectively; \( P = 0.086 \)). The staining observed was predominantly cytoplasmic for all antibodies (Fig. 2).

These values indicate that IGFBP3 and IGFBP5 are decreased in CA125 nonprogressive tumors, whereas IGFBP4 is increased. IGFBP1, IGFBP2, and IGFBP6 are not differentially expressed. The results are consistent with estrogen-regulating expression and, indeed, growth in the letrozole responding tumors.

Because IGFBP3 and IGFBP5 are reduced in nonprogressive tumors, whereas IGFBP4 is increased, it is interesting to compare combinations of these with the outcome, particularly to try and exploit the inverse direction of E2 modulation that exists between IGFBP4 and IGFBP3 or IGFBP5. In CA125 nonprogressors, the immunoscore of IGFBP3 was lower than IGFBP4 in 12 of 15 CA125 nonprogressors and higher in 22 of 24 tumors from CA125 progressors (\( P < 0.0001 \), Fisher’s exact test; Fig. 4). Similarly, the immunoscore of IGFBP5 was lower than IGFBP4 in 8 of 15 nonprogressors and higher in 25 of 26 tumors from CA125 progressors (\( P = 0.0005 \); Fisher’s exact test; Fig. 4). These differential changes could provide an index of IGFBP3-IGFBP4 or IGFBP5-IGFBP4 that could have predictive value.

**Coexpression of IGFBP family members in ovarian cancers.** The coexpression of family members was next analyzed in this set of tumors (Table 2). IGFBP1, IGFBP2, and IGFBP6 were observed to be significantly coexpressed in these tumors, as were IGFBP3 and IGFBP5. It is interesting that these former three are unaffected by E2, whereas the latter two are both downregulated. Further analysis of the IGFBP3 and IGFBP5 comparison revealed that although the 39 paired comparison overall was highly significant (\( P < 0.0001 \)), the association was markedly significant in the CA125 nonprogressors (\( n = 15 \) pairs, \( P < 0.0001 \)) but random in the CA125 progressors (\( n = 24 \) pairs, \( P = 0.52 \)). We speculate that this is consistent with E2 modulating expression down only in responding tumors.

IGFBP4 was associated only with IGFBP2. The strongest associations were between IGFBP3 and IGFBP5 and between IGFBP1 and IGFBP2.

**Prediction of response.** Multivariate logistic regression was conducted on the data set to determine which markers provided independent prediction of progression or not during letrozole therapy. IGFBP and ERα scores were dichotomized at their median values. IGFBP3 was the most powerful predictor of lack of progression, with only ERα status significantly adding to its predictive power (\( P = 0.05 \)). The only other significant combinations were any two of ERα, IGFBP4, and IGFBP5, all of which were inferior to IGFBP3 alone. The combination of IGFBP4, IGFBP5, and ERα was superior to IGFBP3 but still inferior to that obtained with both IGFBP3 and ERα.

**Association of IGFBP expression with other signaling components.** We have previously identified several other predictive markers in this series of tumors which were critical to signaling, namely, ERα, epidermal growth factor receptor, and erbB2 (5). A higher expression of ERα is linked to letrozole response, and this is inversely associated with IGFBP3 expression but not with other family members (Table 2). Similarly, expression of ErbB2 is associated with both IGFBP3 and IGFBP5 expressions. Expression of the epidermal growth factor receptor is associated with IGFBP4 but not with other family members.

**Discussion**

We show in this study that estrogen modulates the expression of the IGFBP isoforms IGFBP3, IGFBP4, and IGFBP5 in ER-positive ovarian cancer cells in culture. These effects are mimicked by the ERα agonist propyl pyrazole triol and are reversed by tamoxifen consistent with ERα mediating this effect. Furthermore, no effects are seen in an ER-negative model. In contrast, IGFBP1, IGFBP2, and IGFBP6 are not modulated

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**Fig. 2.** Immunohistochemical expression of IGFBP family members in ovarian cancer sections. Ovarian cancer sections were stained with antibodies specific for individual isoforms as described in Materials and Methods.
by E₂. We have previously shown that ERα mediates the growth effects of E₂ in the PE04 cell line, with propyl pyrazole triol also stimulating growth, whereas tamoxifen reverses the effect (4).

Extension into primary tumor tissue from patients with ovarian cancers treated with letrozole showed expression patterns consistent with this pattern of regulation. If letrozole-sensitive tumors are estrogen-driven, then we would anticipate that IGFBP4 would be up-regulated and IGFBP3 and IGFBP5 would be down-regulated in such tumors relative to unresponsive tumors. This was found to be the case. Association of IGFBP expression with outcome has significance from two perspectives. The first is that these data supports the view that estrogen regulates gene expression and likely growth in certain of these ER-positive tumors. Secondly, these markers could help provide a predictive signature of outcome defining the subset of cancers that are most likely to be sensitive to letrozole and help target this approach more effectively. We have previously shown that expression of progesterone receptor, combined with expression of ERα, showed significant association with outcome (7); however, the IGFBPs seem to be more powerful predictors. Prospective studies are now required to compare and confirm the predictive power of these biomarkers.

IGFBP3, IGFBP4, and IGFBP5 are most clearly predictive of endocrine response in these ovarian cancers, and this is consistent with previous literature reports of estrogen regulation in breast cancer. The results obtained here with estrogen and anti-estrogens in PE04 cells parallel those found in ER-positive MCF-7 breast cancer cells, in which E₂ down-regulated IGFBP3, whereas the pure antiestrogen ICI 182,780 (faslodex, fulvestrant) up-regulated the protein (24). In breast cancers, expression of IGFBP3 has been reported to be inversely associated with ERα and we observed a similar association here in ovarian cancer (25). Estrogen has been shown to increase IGFBP4 in MCF-7 and other ER-positive breast cancer cell lines (26, 27), whereas ICI 182,780 has the opposite effect (27). Analysis of the IGFBP4 promoter region has identified two Sp1 binding sites used by ERα in this regulation (11).

**Table 1. Association of IGFBP expression with CA125 outcome**

<table>
<thead>
<tr>
<th>IGFBP</th>
<th>CA125 response/stable</th>
<th>CA125 progression</th>
<th>P*</th>
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<tbody>
<tr>
<td>IGFBP1</td>
<td>22</td>
<td>26</td>
<td>0.653</td>
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<tr>
<td>IGFBP2</td>
<td>92</td>
<td>71</td>
<td>0.212</td>
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<tr>
<td>IGFBP3</td>
<td>60</td>
<td>121</td>
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<td>IGFBP4</td>
<td>142</td>
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<tr>
<td>IGFBP5</td>
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<td>204</td>
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<tr>
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<td>108</td>
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*Mann-Whitney test.*
MCF-7 cells, IGFBP5 is down-regulated by estrogen and up-regulated by ICI 182,780 (12). Both IGFBP3 and IGFBP5 have direct inhibitory effects independent of IGF binding, and functional roles for both IGFBP3 and IGFBP5 have been described in ER-positive MCF-7 breast cancer cells. Recombinant IGFBP3 inhibited basal and E₂-stimulated MCF-7 proliferation, whereas an antisense oligonucleotide abolished antiestrogen-induced growth inhibition (24). Similarly, a targeted antisense to IGFBP5 can inhibit the growth effects of estrogen and antiestrogens, and this protein has been proposed to play a role in modulation of proliferation (12). In ovarian cancers, IGFBP3 has been associated with disease stage and residual tumor volume when measured by ELISA or by quantitative reverse transcription-PCR (28–30). IGFBP5 has been shown to be overexpressed in high-grade serous ovarian carcinomas, and a role has been proposed in this histology (31). We observed that these two isoforms were strongly coexpressed in this series of tumors, but only in tumors that were letrozole responsive. We have also begun to link IGFBP isoform expression with expression of other molecules critical to ERα signaling, such as the epidermal growth factor receptor and erbB2. And because these receptors are coexpressed with different isoforms, there may be functional interactions between these pathways. The association between IGFBP3 and with ERα expression, but not with IGFBP5 and IGFBP4, despite their respective relationships with HER2 and EGFR expression, suggests that multiple factors are regulating the IGFBPs in addition to estrogen.

Although endocrine therapy is used by some clinicians in the treatment of ovarian cancer, it is still not well established partially because of the relatively low-response rate and also the lack of useful markers to identify the sensitive subgroup in unselected patients. Our initial phase II trial with letrozole (7) was the first estrogen-targeted trial in ovarian cancer, to our knowledge, to identify a statistically significant association between ERα expression and outcome, although larger trials with tamoxifen have suggested a link with ER expression (5, 6). Predictive markers, such as these IGFBPs, could therefore help identify patients at the outset who have the greatest likelihood of response.

| Table 2. Coexpression of IGFBP family members and association with ERα, HER2, and HER1 |
|----------------------------------|-------------------|-------------------|-------------------|-------------------|
| P for correlation*               | IGFBP1 | IGFBP2 | IGFBP3 | IGFBP4 | IGFBP5 | IGFBP6 |
| IGFBP1                           | 0.0009 | 0.55  | 0.35  | 0.99  | 0.046 | 0.99  |
| IGFBP2                           | 0.0009 | —     | 0.39  | 0.011 | 0.49  | 0.026 |
| IGFBP3                           | 0.55  | 0.39  | —     | 0.11  | <0.0001 | 0.19 |
| IGFBP4                           | 0.35  | 0.011 | —     | —     | 0.72  | 0.72  |
| IGFBP5                           | 0.99  | 0.49  | <0.0001 | 0.72  | —     | 0.61  |
| IGFBP6                           | 0.046 | 0.026 | 0.19  | 0.72  | 0.61  | —     |
| ERα                              | 0.28  | 0.57  | 0.028 | 0.18  | 0.95  | 0.078 |
| HER2                             | 0.32  | 0.23  | 0.021 | 0.82  | 0.046 | 0.50  |
| HER1                             | 0.22  | 0.061 | 0.21  | 0.024 | 0.45  | 0.50  |

*Pearson correlation.
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