TIG1 Promotes the Development and Progression of Inflammatory Breast Cancer through Activation of Axl Kinase

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Abstract

Inflammatory breast cancer (IBC) is the most lethal form of breast cancer, but the basis for its aggressive properties is not fully understood. In this study, we report that high tumoral expression of TIG1 (RARRES1), a functionally undefined membrane protein, confers shorter survival in patients with IBC. TIG1 depletion decreased IBC cell proliferation, migration, and invasion in vitro and inhibited tumor growth of IBC cells in vivo. We identified the receptor tyrosine kinase, Axl, as a TIG1-binding protein. TIG1 interaction stabilized Axl by inhibiting its proteasome-dependent degradation. TIG1-depleted IBC cells exhibited reduced Axl expression, inactivation of NF-κB, and downregulation of matrix metalloproteinase-9, indicating that TIG1 regulates invasion of IBC cells by supporting the Axl signaling pathway in IBC cells. Consistent with these results, treatment of IBC cells with the Axl inhibitor SGI-7079 decreased their malignant properties in vitro. Finally, TIG1 expression correlated positively with Axl expression in primary human IBC specimens. Our findings establish that TIG1 positively modifies the malignant properties of IBC by supporting Axl function, advancing understanding of its development and rationalizing TIG1 and Axl as promising therapeutic targets in IBC treatment. Cancer Res; 73(21); 6516–25. ©2013 AACR.

Introduction

Inflammatory breast cancer (IBC) is the most lethal and aggressive form of breast cancer (1). Despite progress in combined modality treatment (chemotherapy, surgery, and radiation therapy), the long-term outcome of patients with IBC remains poor (2). IBC is also associated with a high risk of developing distant metastases, which is related to the lower survival rate of patients with IBC (3).

Efforts to unravel the molecular mechanism for the tumorigenicity and metastasis of IBC have yielded some successes such as the identification of several molecular changes, including loss of WISP3 and overexpression of Bho GTPase (4), E-cadherin (5), angiogenic factors (6), and translation initiation factor eIF4GI (7). Our previous results indicated that the EGF receptor pathway is involved in tumor growth and metastasis of IBC (8). A recent study showed that the metastatic, aggressive behavior of IBC may be mediated by a cancer stem cell component that displays aldehyde dehydrogenase 1 enzymatic activity (9). Although these findings have improved our understanding of IBC, the molecular mechanism underlying the aggressiveness of IBC is not well understood, and effective targeted therapies for this disease remain limited.

Tazarotene-induced gene 1 (TIG1), also known as retinoic acid receptor responder 1, is one of the genes highly upregulated in skin raft cultures by tazarotene (10), a synthetic retinoid. TIG1 protein contains a single membrane-spanning hydrophobic region and has been predicted to be a transmembrane protein. TIG1 resembles CD38, a retinoid-responsive molecule in immune cells, and might be structurally related to and analogous in function to CD38 (11). The expression of TIG1 in many tumor tissues and cell lines, including prostate cancer (12), endometrial cancer (13), and head and neck cancer (14), is lost or silenced by hypermethylation of its promoter. TIG1 has been reported to be a potential tumor suppressor gene in human prostate cancer and endometrial cancer (12, 13).

The function of TIG1 in breast cancer is unknown. Recently, we identified TIG1 as a potentially druggable gene that is highly expressed in triple-negative breast cancer and IBC in particular. By analyzing TIG1 gene expression in patients with IBC and tumor-node-metastasis stage-matched non-IBC (15) and three independent non-IBC prognostic sets (WANG; ref. 16; TRANSBIG; ref. 17; and MAINZ; ref. 18), we found that in both IBC and non-IBC datasets, triple-negative breast cancer samples had significantly higher expression of TIG1 than did other clinical subtypes (estrogen receptor (ER) positive/HER2

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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negative, and HER2 positive). These findings raised the possibility that TIG1 may contribute to the aggressiveness of IBC, which drove us to investigate the role of TIG1 in the pathogenesis of IBC. In the study reported here, we showed that TIG1 correlates with shorter survival of patients with IBC and promotes tumor growth and invasion of IBC cells. We also identified the receptor tyrosine kinase Axl as a functional partner of TIG1 in IBC cells and revealed a mechanism that links TIG1 to the Axl gene in IBC.

Materials and Methods

Cell lines, reagents, and antibodies

SUM149 human IBC cells were purchased from Asterand. KPL-4 IBC cells were a kind gift from Dr. Junichi Kurebayashi (Kawasaki Medical School, Kawasaki, Japan). SUM149 and KPL-4 cells were validated using a short tandem repeat method based on primer extension to detect single base deviations in October 2010 and July 2013, respectively, by the Characterized Cell Line Core Facility at MD Anderson Cancer Center (Houston, Texas). SUM149 cells were cultured in Ham's F-12 medium supplemented with 5% FBS (Life Technologies, Inc.), 5 μg/mL insulin, and 1 μg/mL hydrocortisone. KPL-4 cells were grown in Dulbecco's Modified Eagle Medium/F-12 medium supplemented with 10% FBS. The following primary antibodies were used: anti-TIG1 (R&D Systems), anti-Axl, anti-β-actin or -α-tubulin (Sigma-Aldrich Chemical Co.), anti-phospho-Axl (Tyr702) and anti-MMP-9 (Cell Signaling Technology), anti-Myc (Roche), anti-PCNA (Abcam), anti-lamin B (Calbiochem), anti-p65, anti-TIG1 (sc-98965), and anti-Axl (sc-20741; Santa Cruz Biotechnology). The secondary fluorescent antibodies for Western blotting and immunofluorescence were from Molecular Probes and Invitrogen, respectively. Axl inhibitor SGI-7079 was provided by Tolero Pharmaceuticals, Inc.

All transfections were conducted with FuGENE HD transfection reagent (Roche) following the manufacturer's guidelines.

Immunohistochemical staining and evaluation

Tissues from 88 patients with primary IBC who were treated at The University of Texas MD Anderson Cancer Center from September 1994 to August 2004 were included in this study. This study was approved by the MD Anderson Cancer Center Institutional Review Board. Immunohistochemical (IHC) staining was conducted as described previously (19). An evaluation of the IHC results is described in detail in the Supplementary Materials and Methods.

Xenograft studies

Animal care and use were in accordance with institutional and NIH guidelines. The xenograft mouse model is described in the Supplementary Materials and Methods.

Proliferation, BrdUrd incorporation, migration, and invasion assays, anchorage-independent growth, and cell-cycle analysis

These assays are described in detail in the Supplementary Materials and Methods.

DNA microarray analysis

siRNA transfection, RNA isolation, cDNA microarray, gene expression analysis, and statistical analysis were conducted as described in the Supplementary Materials and Methods. The microarray dataset has been deposited in the NCBI Gene Expression Omnibus database (http://www.ncbi.nlm.nih.gov/geo) with the accession number GSE30543.

Immunoblotting, immunoprecipitation, and cellular fractionation

These assays were conducted as described in the Supplementary Materials and Methods.

Quantitative reverse transcription PCR

Total RNA was extracted and purified using an RNeasy mini kit (Qiagen, Inc.) according to the manufacturer's instructions. The quantitative reverse transcription (qRT)-PCR reactions were conducted using an iScript One-Step RT-PCR kit with SYBR Green (Bio-Rad). Human β-actin mRNA was used as a normalization control. Primer sequences for TIG1, Axl, and β-actin are described in the Supplementary Materials and Methods.

Confocal microscopy and immunofluorescence assay

These assays are described in detail in the Supplementary Materials and Methods.

Statistical analysis

The two-sided unpaired Student t test was used for comparison between groups. Statistical analysis of the correlation between TIG1 expression and IBC patient survival (months) was conducted using the two-tailed unpaired Student t test. The correlation between TIG1 and Axl expression in IBC tissues was conducted by using Spearman rank correlation coefficient. P < 0.05 was considered statistically significant.

Results

TIG1 is associated with shorter median survival in IBC patients

To assess the role of TIG1 in IBC pathogenesis and progression, we investigated TIG1 expression in three IBC cell lines, SUM149 (ER negative/HER2 negative: ref. 20), KPL-4 (ER negative/HER2 positive: ref. 21), and SUM190 (ER negative/HER2 positive: ref. 20), and in IBC patient tissues. Our data showed that TIG1 was highly expressed in two of the three IBC cell lines, SUM149 and KPL-4, but not in IBC cell line SUM190, the non-IBC cell lines, or normal human mammary epithelial cell line MCF-10A (Fig. 1A). No staining of TIG1 was observed in normal breast tissues; however, the majority of IBC cases (56 of 76 cases, 73.7%) were TIG1 positive with high staining intensity (Fig. 1B). We observed a significant association between high TIG1 expression and a relatively worse clinical outcome in these patients with IBC who had had preoperative chemotherapy (Fig. 1C, unpaired t test; P = 0.0369). There were no significant associations between TIG1 expression and other important clinicopathologic factors, such as age at diagnosis, lymph node status, histologic type, lymphovascular invasion,
Proliferation of SUM149 TIG1 stable knockdown clones, assessed the effect of TIG1 silencing on IBC cell proliferation. Silencing endogenous TIG1 reduces proliferation of IBC cells and inhibited tumor growth in an IBC xenograft model.

Silencing endogenous TIG1 reduces migration and invasion of IBC cells \textit{in vitro}

Because patients with IBC are at high risk of recurrence in the form of metastatic disease, we investigated the effect of TIG1 knockdown on cell migration and invasion. Compared with migration and invasion of shControl cells, migration and invasion of shTIG1-A cells were reduced by 41% \((P < 0.001)\) and 49% \((P < 0.001)\), respectively, and migration and invasion of shTIG1-D cells were reduced by 39% \((P < 0.001)\) and 48% \((P < 0.001)\), respectively (Fig. 2F and G). We compared cell growth rates and found that TIG1 depletion did not cause a significant decrease in cell numbers within 24 hours (Supplementary Fig. S1A and S1B). Migration and invasion assays were conducted within 6 and 18 hours, respectively, indicating that the slower rates of migration and invasion of TIG1-depleted cells were not caused by slower cell division. Similar results were observed in IBC KPL-4 cells (Supplementary Fig. S2C and S2D). To determine whether TIG1 knockdown affects the reorganization of the actin cytoskeleton, we used rhodamine-phalloidin to stain F-actin filaments in SUM149, shControl, and TIG1 knockdown cells. As shown in Fig. 2H, F-actin filaments were arranged into typical stress fibers in most of the parental or shControl cells. However, very few or no stress fibers were observed in the TIG1 knockdown cells; instead, phalloidin staining was diffusely distributed throughout the cytoplasm. Our data indicate that TIG1 knockdown in SUM149 cells impaired stress fiber formation. Moreover, TIG1-depleted shTIG1-A and shTIG1-D cells lost the ability to grow into Matrigel and showed an epithelial cell phenotype, which further supports the concept that TIG1 regulates the invasion of IBC cells (Supplementary Fig. S3). Taken together, these results indicated that silencing endogenous TIG1 reduced migration and invasion of IBC cells \textit{in vitro}.

ER status, progesterone receptor status, and HER2 status (Supplementary Table S1). Taken together, the high expression of TIG1 in human IBC patient tissues and cell lines and its positive correlation with poor clinical outcome of IBC patients indicated that TIG1 may contribute to the aggressiveness of IBC.

Silencing endogenous TIG1 reduces proliferation of IBC cells \textit{in vitro} and inhibits tumor growth in a xenograft model

To investigate the role of TIG1 in IBC progression, we first assessed the effect of TIG1 silencing on IBC cell proliferation. Proliferation of SUM149 TIG1 stable knockdown clones, shTIG1-A and shTIG1-D, was decreased by 38% \((P < 0.001)\) and 25% \((P = 0.001)\), respectively, compared with proliferation of shControl cells (Fig. 2A and B). Time-course cell prolifera-

Figure 1. TIG1 is highly expressed in human IBC tissues and cell lines and correlates with poor median survival of patients with IBC. A, the expression of TIG1 was tested with Western blotting in three IBC cell lines, 10 non-IBC cell lines, and a normal human mammary epithelial cell line (MCF-10A). B, representative IHC staining of TIG1 protein in IBC tissues (top) and normal breast tissue (bottom). Scale bars, 50 μm. Quantitative results are shown in right panel. C, box plot of survival (months) of patients with IBC with high or low TIG1 expression. Boxes include values in the 25% to 75% interval; central lines represent the median value; whiskers show the lowest and highest values. \(P = 0.0369\).
Figure 2. Silencing endogenous TIG1 in SUM149 IBC cells inhibits cell proliferation, migration, invasion in vitro, and tumor growth in a xenograft model. 

A, SUM149 cells were transfected with control (shControl) or TIG1-targeted (shTIG1-A and shTIG1-D) shRNAs. Expression of TIG1 in parental SUM149 cells and in the stable clones shControl, shTIG1-A, and shTIG1-D was analyzed by Western blotting. B, proliferation of TIG1 shRNA knockdown cells was compared with that of control shRNA knockdown cells by using the Trypan blue exclusion assay. Experiments were independently repeated three times. Bars, ± SD. *, P < 0.001; **, P = 0.001. C, tumor growth of TIG1 knockdown shTIG1-A and shTIG1-D cells was compared with that of control shRNA knockdown cells and those injected with SUM149 cells, P < 0.001. Bars, ± SD. D, expressions of TIG1 in tumor samples from each mouse were analyzed with Western blotting. E, representative images of immunofluorescence staining of tumor tissues with TIG1, Axl, and PCNA antibodies. Scale bar, 200 μm. The relative fluorescence intensity from the images is shown in the bottom panel. Bars, ± SD. F, shRNA-transfected SUM149 cells were analyzed for Transwell migration by crystal violet staining (top); quantitative results are shown in the bottom panel. Experiments were independently repeated three times. Bars, ± SD. *, P < 0.001. G, shRNA-transfected SUM149 cells were analyzed for invasion through Matrigel by crystal violet staining (top); quantitative results are shown in the bottom panel. Experiments were independently repeated three times. Bars, ± SD. *, P < 0.001. H, SUM149 and shRNA-transfected SUM149 cells were analyzed for actin organization by immunofluorescence analysis using rhodamine-phalloidin (F-actin, red). Nuclei were labeled with 4′,6-diamidino-2-phenylindole (DAPI; blue). Scale bar, 10 μm.
TIG1 restoration rescues the effects of TIG1 depletion cells

To further confirm the function of TIG1 in IBC cells, we restored TIG1 expression in TIG1-depleted shTIG1-A cells and found that the proliferation of TIG1-restored pCMV6-TIG1 cells increased by 52.3% ($P < 0.005$), and their migration and invasion increased by 62.6% ($P < 0.001$) and 41.3% ($P = 0.001$), respectively, compared with shTIG1-A cells (Fig. 3A–D). The rescue effect of TIG1 restoration confirmed the contribution of TIG1 to the proliferation and invasion of IBC cells.

Receptor tyrosine kinase Axl is a functional partner of TIG1

To investigate the underlying mechanism by which TIG1 promotes tumor growth and invasion of IBC cells, we compared gene expression profiles between SUM149 cells transfected with control siRNA and SUM149 cells transfected with siRNA-targeting TIG1 using DNA microarray analysis. We selected, as candidates, 19 representative genes related to proliferation, migration, and invasion from 183 probe sets with at least two-fold change in expression ($P < 0.005$, two-sample $t$ test; Supplementary Table S2 and Supplementary Fig. S4). We further validated the downregulation of one candidate, receptor tyrosine kinase Axl, in TIG1-depleted shTIG1-A and shTIG1-D cells at the mRNA (Fig. 4A, left) and protein levels (Figs. 4A, right and S5B) and in tumors produced by injection of TIG1-depleted cells (Fig. 2E).

To test whether Axl is a potential functional partner of TIG1, we restored Axl expression in TIG1-depleted shTIG1-A cells and found that it rescued the reduction in proliferation (19.0% rescued; $P < 0.005$), migration (87.4% rescued; $P < 0.001$), and invasion (79.1% rescued; $P < 0.001$) of shTIG1-A cells due to TIG1 silencing (Fig. 4B–E and Supplementary Fig. S5A and S5B). Furthermore, depletion of Axl (shAxl-D and shAxl-E cells) has the same effects on the proliferation [38.5% reduced by shAxl-D ($P < 0.005$) and 48.8% reduced by shAxl-E ($P = 0.001$)], migration [32.7% reduced by shAxl-D ($P < 0.001$) and 31.7% reduced by shAxl-E ($P < 0.001$)], and invasion [36.7% reduced by shAxl-D ($P < 0.001$) and 39.8% reduced by shAxl-E ($P < 0.001$)] of SUM149 cells as those of TIG1 depletion (Fig. 4F–I). Given that...
Ax1 restoration rescued the effects of TIG1 silencing and given that Ax1 depletion had the same effects as TIG1 depletion, we confirmed Ax1 as a potential functional partner of TIG1 in IBC cells.

We further examined the correlation between TIG1 and Ax1 expression in the same panel of IBC patient samples as shown in Fig. 1B and C. We found that TIG1 expression was positively correlated with Ax1 expression in IBC patient samples (Fig. 4J and Table 1). Taken together, these data further suggest a link between TIG1 and Ax1 expression in the regulation of IBC progression.

TIG1 interacts with Ax1 and stabilizes Ax1

To elucidate the link between TIG1 and Ax1 in the regulation of IBC progression, we first examined a possible interaction between TIG1 and Ax1 by reciprocal immunoprecipitation followed by immunoblotting analysis. Our results showed that endogenous TIG1 was specifically associated with Ax1 in vivo (Fig. 5A). We further detected the colocalization of TIG1 with Ax1 in SUM149 cells transfected with control short hairpin RNA (shRNA) but not with shRNA-targeting TIG1 (Fig. 5B). We also detected colocalization of TIG1 with Ax1 in KPL-4 cells (Supplementary Fig. S6). We further found that cotransfection of the pCMV6-TIG1 vector with the pCMV6-Ax1 vector in 293T
cells increased the expression of Axl in a dose-dependent manner (Fig. 5C). Degradation of Axl has been proven to be metalloproteinase and proteasome dependent (22). Treatment with the proteasome inhibitor MG-132 fully restored Axl expression in TIG1-depleted shTIG1-A and shTIG1-D cells (Fig. 5D), indicating that TIG1 can stabilize Axl protein in vivo by inhibiting its proteasome-dependent degradation.

**TIG1 regulates invasion of IBC cells through the Axl signaling pathway**

Enhanced expression of matrix metalloproteinase (MMP)-9 is required for Axl-mediated invasion both in vitro and in vivo, and NF-κB signaling is found to be involved in Axl-enhanced MMP-9 activation (23). As shown in Fig. 5E, the MMP-9 level in TIG1-silenced clones, shTIG1-A and shTIG1-D, were
significantly lower than those in parental SUM149 or shControl cells. We also found that the nuclear accumulation of p65, an indicator of activation of NF-κB regulation, was significantly abolished in TIG1-depleted shTIG1-A and shTIG1-D cells (Fig. 5F). Taken together, the impact of TIG1 depletion on downstream molecules MMP-9 and NF-κB of the Axl signaling

Table 1. TIG1 expression positively correlates with Axl expression in IBC patient samples

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<th>TIG1 Expression</th>
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<td>Axl Expression</td>
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NOTE: Expression patterns of TIG1 and Axl in IBC patient samples were determined and summarized. The correlation between TIG1 and Axl was analyzed using Spearman rank correlation coefficient (P < 0.005).
pathway suggests that TIG1 may regulate the invasion of IBC cells through the Axl signaling pathway.

Inhibition of the Axl signaling pathway reduces proliferation, migration, and invasion of IBC cells

To investigate the clinical relevance of our findings, we tested the effects of an Axl inhibitor, SGI-7079 (24), in IBC cells. SGI-7079 treatment inhibited the phosphorylation of Axl at Tyr 702 upon Gaα6 stimulation in SUM149 cells (Fig. 6A). SGI-7079 significantly inhibited the proliferation of SUM149 or KPL-4 cells with an IC50 of 0.43 or 0.16 μM/L, respectively, and induced sub-G1 cell-cycle arrest (Fig. 6B and C). The growth of SUM149 and KPL-4 in soft agar, one of the hallmark characteristics of cellular transformation and uncontrolled cell growth, was also significantly inhibited by SGI-7079 treatment (Fig. 6D). SGI-7079 treatment also significantly decreased the migration and invasion of SUM149 cells (Fig. 6E) and the invasion of KPL-4 cells (Supplementary Fig. S7). Taken together, Axl inhibitor SGI-7079 significantly inhibited the proliferation, migration, and invasion of IBC cells, suggesting that Axl may be a promising therapeutic target in patients with IBC.

Discussion

In this study, we determined the contribution of a novel oncogenic gene, TIG1, to tumor growth and invasion of IBC cells. The capacity to migrate and invade through tissue barriers is essential for cancer cells to complete the process of metastasis (25). The contribution of TIG1 to the invasion of IBC suggests that TIG1 might play a role in metastasis. The tumorigenic and potential metastatic function of TIG1 revealed in our study may be cancer-type specific. Previous reports showed that TIG1 is a tumor suppressor in other cancer types, such as prostate cancer and endometrial cancer (12, 13). In contrast with those reports, we observed high-expression frequency of TIG1 protein in IBC specimens and cell lines and noted the inhibitory effects of TIG1 depletion on cell proliferation and tumor growth of IBC. These results indicate that TIG1 contributes to tumor growth of IBC.

The most important finding in our study was the statistically significant correlation between high TIG1 expression and poorer patient median survival seen in the box and whisker plot. Ideally, we would have confirmed this correlation using other standard plotting methods, such as the widely used Kaplan–Meier method. However, our small patient sample size (88 samples) and the censoring of some survival data in our sample rendered these methods less informative than they would be in a larger population. Using the box and whisker plot as an exploratory method, however, we showed a correlation between TIG1 expression (after chemotherapy) and IBC patient median survival duration, which suggests the contribution of TIG1 to the malignant process of IBC and the importance of determining whether TIG1 serves as a prognostic marker for patients with IBC using preoperative chemotherapy samples in a future investigation.

Among the other interesting findings in this study were the identification of a linkage between TIG1 and the Axl signaling pathway, a critical element in the signaling network regulating migration and invasion of breast cancer cells. Our results indicated that TIG1 stabilizes Axl by inhibiting the proteasome-dependent degradation of Axl. TIG1 depletion down-regulates Axl expression and inactivates NF-κB, which leads to downregulation of MMP-9, ultimately leading to decreased invasion of IBC cells. These results suggest that TIG1 regulates the invasion of IBC cells through mediation of the Axl signaling pathway. The positive correlation between TIG1 and Axl expression in IBC patient samples revealed in our study further supports the importance of TIG1 and Axl linkage in the regulation of IBC progression. To our knowledge, this is the first report to describe the mechanism by which TIG1 promotes invasion of IBC cells and the signaling pathway that TIG1 participates in.

The identification of Axl as a functional partner of TIG1 suggests that Axl might be a potential target for therapeutic intervention in IBC. Thus, blocking the Axl signaling pathway may inhibit the growth and invasion of IBC cells. Indeed, our data showed that depleting Axl with the use of shRNA and inhibiting the tyrosine kinase activity of Axl with the use of the small-molecule inhibitor SGI-7079 significantly decreased the proliferation, migration, and invasion of IBC cells, suggesting that Axl is a promising therapeutic target in patients with IBC. Moreover, the tumorigenic function of TIG1 revealed in this study suggests that TIG1 might be an attractive therapeutic target for the treatment of IBC, which will be investigated in future studies by delivering neutral liposome (DOPC)-encapsulated TIG1 siRNA to tumors to determine whether it can inhibit tumor growth in an IBC xenograft model.

In summary, our findings show that TIG1 plays an important role in the pathogenesis of IBC by promoting tumor growth and invasion through the oncogenic gene Axl and furthermore, that TIG1 and Axl are promising therapeutic targets in patients with IBC.

Disclosure of Potential Conflicts of Interest

D.J. Bearss is employed as founder shareholder and has ownership interest (including patents) in Tolero Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: X. Wang, Y. Gong, S.L. Warner, D.J. Bearss, N.T. Ueno
Development of methodology: X. Wang, N.T. Ueno
Acquisition of data (provided animal, obtained and managed patients, provided facilities, etc.): H. Saso, W. Xia, Y. Gong, M.-C. Hung, N.T. Ueno
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): X. Wang, H. Saso, T. Iwamoto, Y. Gong, S.L. Warner, G.N. Hortobagyi, N.T. Ueno
Writing, review, and/or revision of the manuscript: X. Wang, T. Iwamoto, Y. Gong, L. Pusztai, W.A. Woodward, J.M. Reuben, S.L. Warner, G.N. Hortobagyi, N.T. Ueno
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Saso, G.N. Hortobagyi
Study supervision: N.T. Ueno

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Role of TIG1 in Tumorigenicity and Invasion of IBC

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