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Priority Report

Cancer Research

FOXC1 Is a Potential Prognostic Biomarker with Functional Significance in Basal-like Breast Cancer

Partha S. Ray[1], Jinhua Wang[2], Ying Qu[2,5], Myung-Shin Sim[3], Jaime Shamonki[4], Sanjay P. Bagaria[1], Xing Ye[3], Bingya Liu[5], David Elashoff[6], Dave S. Hoon[2], Michael A. Walter[7], John W. Martens[8], Andrea L. Richardson[9], Armando E. Giuliano[1], and Xiaojiang Cui[2]

Abstract

Gene expression signatures for a basal-like breast cancer (BLBC) subtype have been associated with poor clinical outcomes, but a molecular basis for this disease remains unclear. Here, we report overexpression of the transcription factor FOXC1 as a consistent feature of BLBC compared with other molecular subtypes of breast cancer. Elevated FOXC1 expression predicted poor overall survival in BLBC (P = 0.0001), independently of other clinicopathologic prognostic factors including lymph node status, along with a higher incidence of brain metastasis (P = 0.02) and a shorter brain metastasis–free survival in lymph node–negative patients (P < 0.0001). Ectopic overexpression of FOXC1 in breast cancer cells increased cell proliferation, migration, and invasion, whereas shRNA-mediated FOXC1 knockdown yielded opposite effects. Our findings identify FOXC1 as a theranostic biomarker that is specific for BLBC, offering not only a potential prognostic candidate but also a potential molecular therapeutic target in this breast cancer subtype. *Cancer Res; 70(10); 3870–6. ©2010 AACR.*

Introduction

Molecular classification of breast cancer has identified specific subgroups with clinical and biological implications (1). Basal-like breast cancers (BLBC), which express genes characteristic of basal/myoepithelial cells in the normal mammary gland, compose up to 15% of all breast cancers (2). BLBCs underexpress estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) and encompass 60% to 90% of triple-negative (ER^-/PR^-/$HER2^-$) breast cancers. Whereas ER and HER2 guide treatment of luminal and HER2 breast cancers, respectively, chemotherapy is still the only modality of systemic therapy for BLBC. Preferentially affecting younger women, particularly African American women, BLBCs are associated with high histologic grade, aggressive clinical behavior, and a high rate of metastasis to the brain and lung (3). Unlike other breast cancer subtypes, there seems to be no correlation between tumor size and lymph node metastasis in BLBCs (4).

BLBCs are associated with expression of basal cytokeratins (CK5/6, CK14, and CK17), epidermal growth factor receptor (EGFR), c-kit, and p53 and absence of ER, PR, and HER2, and thus have been defined differently in different studies using a set of diagnostic markers. Whereas Nielsen et al. defined BLBC on the basis of negative ER and HER2 expression and positive basal cytokeratin, EGFR, and/or c-kit expression (5), other groups used the combination of negative ER and HER2 expression and positive CK5, P-cadherin, and p63 expression (6) or positive vimentin, EGFR, and CK5/6 expression (7). These different technical approaches in combination with widely varying patient cohorts may explain the inconsistent experimental results for these markers.

To identify specific biomarkers for BLBC, we set out to systematically analyze the 306-member intrinsic gene set (IGS; ref. 8), as well as other reported individual markers for BLBC using multiple microarray data sets. Degree of correlation of each individual gene with the basal-like subtype based on mRNA expression was used to identify genes highly specific to BLBC. The FOXC1 transcription factor emerged as a top-ranking gene. We then assessed the diagnostic and prognostic significance of FOXC1 and further characterized the role of FOXC1 in regulating cellular functions in breast cancer.

Materials and Methods

Analysis of microarray data sets. Probe-level raw expression data from publicly available human breast cancer gene expression microarray data sets (9–18) and the ExpO Project

Authors' Affiliations: Departments of [1]Surgical Oncology, [2]Molecular Oncology, and [3]Biostatistics, John Wayne Cancer Institute; [4]Department of Pathology, St. John's Health Center, Santa Monica, California; [5]Department of Surgery, Ruijin Hospital, Jiaotong University School of Medicine, Shanghai, China; [6]Division of General Internal Medicine, School of Medicine, University of California at Los Angeles, Los Angeles, California; [7]Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada; [8]Department of Medical Oncology, Erasmus Medical Center, Rotterdam, the Netherlands; and [9]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

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P.S. Ray, J. Wang, and Y. Qu contributed equally to this work.

Corresponding Author: Xiaojiang Cui, Department of Molecular Oncology, John Wayne Cancer Institute, Santa Monica, CA 90404. Phone: 310-998-3916; Fax: 310-582-7390; E-mail: cuix@jwci.org.

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database of the International Genomics Consortium (IGC) at https://expo.intgen.org (Supplementary Table S1) were downloaded and analyzed using Genespring GX 10.0 software (Agilent Technologies). A total of 2,073 breast cancer patient samples were analyzed. For microarray raw data obtained from Affymetrix gene chips (8 of 11 data sets), the Robust Multi-chip Averaging algorithm was used. Background correction, normalization, and summarization were performed, followed by baseline transformation to median of all samples from a specific data set on a per gene/per probe set basis. For cDNA microarrays (3 of 11), the publicly available log 2 normalized signal intensity values were directly imported into the Genespring software platform. Molecular subtypes (luminal A/B, HER2, and basal-like) were identified by subjecting all data sets to a hierarchical clustering algorithm by using a Pearson uncentered similarity metric and the average linkage rule based on the IGS (8). Average relative mRNA levels (mean log 2 signal intensity) for the IGS genes and reported markers for BLBC (see Supplementary Methods) were compared between basal-like and pooled non–basal-like groups using the Mann-Whitney test followed by logistic regression analysis (SAS, version 9.1.3) to identify the genes most characteristic of the basal-like group (Supplementary Tables S2–S5). Statistical significance was defined as $P < 0.05$. To determine the correlation between FOXC1 and hormone receptor status, we used a data set that included immunohistochemical status of ER, PR, and HER2 (11). A gene signature associated with FOXC1 expression was developed using stringent, supervised inclusion criteria in five individually analyzed microarray data sets (9, 10, 12, 13). The gene signature was additionally validated in six other microarray data sets (refs. 11, 14–18; see Supplementary Methods).

Survival analysis. Prognostic significance of FOXC1 in predicting overall survival in breast cancer patients was examined in the van de Vijver et al., Herschkowitz et al., Sorlie et al., and Pawitan et al. microarray data sets (14–16, 18). Association with metastasis to the brain or bone was examined in lymph node–negative breast cancer patients in the Wang et al. data set (17). The Wilcoxon rank sum test was used to assess statistical significance for this comparison. Brain-specific and bone-specific metastasis-free survival was also examined in the same data set. Univariate and multivariate analyses were done using log-rank test and Cox regression model, respectively. Variables included in the multivariate analysis were selected based on statistical significance in initial univariate analysis and included age, tumor size, and lymph node status. Survival plots were created using Kaplan-Meier methods.

Immunohistochemistry. A polyclonal FOXC1 antibody (Lifespan Biosciences) was used to determine FOXC1 protein expression in human breast cancer tissue microarrays (BRC961 and BR962, US Biomax) and in 42 archived triple-negative human breast cancer specimens from the John Wayne Cancer Institute tissue bank with Institutional Review Board approval.

FOXC1-knockdown cells. FOXC1 shRNAs and a control shRNA that does not match any known cDNA were from Sigma. Cells were stably transfected with the FOXC1 or the control shRNA construct and selected with 5 μg/mL puromycin. Pooled knockdown cells were used for experiments.

FOXC1-overexpressing cells. A full-length human FOXC1 cDNA was stably transduced into breast cancer cells. Stable cell lines were selected with 800 μg/mL G418. Pooled populations were used for experiments.

Cell culture. Cancer cell lines were from American Type Culture Collection. Normal human mammary epithelial cells (HMEC) were from Clonetics. Cell proliferation was assessed by the MTT assay. Three-dimensional cell culture was done using BD Matrigel matrix in 96-well plates.

Cell migration and invasion assay. Cells were plated on the top of Boyden chamber inserts. Serum (10%) was used as the chemoattractant. Cells on the lower surface of the inserts were stained and counted. For invasion assays, inserts were coated with Matrigel matrix.

Results and Discussion

Gene expression analysis of publicly available human breast cancer microarray data sets revealed that the Forkhead-box transcription factor FOXC1, essential for mesoderm tissue development, had significantly higher expression in the basal-like subgroup than in other subtypes (Fig. 1A and B; Supplementary Figs. S1 and S2A–C). High FOXC1 expression correlated positively and significantly with the basal-like subgroup (Supplementary Tables S2–S5). Elevated FOXC1 mRNA expression was also associated with triple-negative breast cancer, consistent with the notion that 60% to 90% of triple-negative breast cancers are basal-like (Fig. 1C; Supplementary Fig. S2D). A 30-gene FOXC1 signature was derived from correlation with FOXC1 expression in six data sets (Supplementary Table S6) and validated in five separate data sets. These genes displayed an overall expression profile that coincided with the basal-like subgroup clustered by IGS (Fig. 1D; Supplementary Fig. S3). Conversely, hierarchical clustering using the *FOXC1* gene signature identified the same basal-like subgroup determined by IGS (Supplementary Fig. S4). Whereas pathway analysis of this gene signature did not yield a dominant pathway (data not shown), some members such as FABP7, GABRP, EN1, KCNK5, ZIC1, ACTR3B, and FOXC1 are notably involved in brain development and brain tumorigenesis, which might explain why BLBC preferentially metastasizes to the brain.

We then evaluated FOXC1 protein expression using immunohistochemistry on breast cancer tissue microarrays (TMA). Strong nuclear FOXC1 staining was found in triple-negative TMA samples expressing basal cytokeratins ($CK5/6^+$ and/or $CK14^+$; Fig. 2A) but not in non–triple-negative tumors (data not shown). Cytoplasmic staining of FOXC1 was rare, and it was normally concomitant with nuclear staining of FOXC1. This pattern of subcellular localization was confirmed in an independent cohort of 42 archived triple-negative breast cancer specimens. Positive expression of FOXC1 was associated significantly with expression of basal cytokeratins (Fig. 2B) and displayed a sensitivity of 0.81 and a specificity of 0.80 in detecting the basal-like phenotype identified by positive staining of CK5/6 and/or CK14. Absence of CK staining in some

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Figure 1. Differential expression of FOXC1 in human breast cancer subtypes. A, values of normalized signal intensity (baseline-to-zero-transformed) for basal-like subtype–associated genes from the Richardson et al. data set (9). Colors represent different subgroups: green, normal; orange, luminal A/B; blue, HER2; red, basal-like. B, boxplot of FOXC1 values (normalized signal intensity) in normal breast tissue and luminal, HER2, and basal-like tumors of the same data set. Statistical significance was determined using ANOVA. C, boxplot of FOXC1 values from the Hess et al. data set with known ER, PR, and HER2 status (11). See Supplementary Fig. S2A legends for description of boxplots. Statistical significance was determined using ANOVA. D, gene expression heat maps of the Ivshina et al. data set (12) hierarchically clustered by IGS display the expression profile of the FOXC1 signature.

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FOXC1$^+$/ER$^-$/PR$^-$/HER2$^-$ samples in this cohort may reflect inconsistent expression of these cytokeratins in BLBCs defined by expression arrays (5). The finding that nuclear FOXC1 was consistently detected by immunohistochemistry despite its short protein half-life (<30 minutes; ref. 19) may suggest a robust constitutive expression of FOXC1 in BLBC. Analysis of a microarray data set for a human breast cancer cell line panel revealed higher FOXC1 expression in BLBC cell lines (Supplementary Fig. S5), which was confirmed by immunoblotting (Fig. 2C).

The prognostic significance of FOXC1 in breast cancer was next examined in the 295-sample van de Vijver et al. data set (14). In univariate analysis, overall survival was significantly worse in tumors identified using the 30-gene FOXC1 signature ($P = 0.0004$) or using elevated FOXC1 mRNA levels alone ($P = 0.0001$; Fig. 3A). Overall survival decreased by 35% for each unit increase of relative FOXC1 mRNA levels. In multivariate analysis, FOXC1 was an independent prognostic indicator of overall survival after adjusting for clinicopathologic variables such as age, tumor size, and lymph node status (hazard ratio, 1.25; 95% confidence interval, 1.02–1.52; $P = 0.02$). Akaike information criteria (AIC; ref. 20) were used in comparing the fit of the two separate prognostic models after adjusting for clinicopathologic variables. The model based on FOXC1 mRNA expression (AIC, 820.0) was similar to the model based on the IGS-derived basal-like cluster (AIC, 815) in terms of the model fit predicting survival. The association of FOXC1 with overall survival was also shown in the 232-sample Herschkowitz et al. (15), 122-sample Sorlie et al. (16), and 159-sample Pawitan et al. (18) data sets (Supplementary Fig. S6). Furthermore, the *FOXC1* gene signature and mRNA levels, like the basal-like phenotype, allowed prognostic stratification of lymph node–negative breast cancers ($P = 0.0003$) in the van de Vijver et al. data set (ref. 14; Fig. 3B). In addition, elevated FOXC1 expression, which was positively associated with brain metastasis ($P = 0.02$) and inversely associated with bone metastasis ($P = 0.0002$) in the 286-sample Wang et al. data set (17), significantly correlated with shorter brain metastasis–free survival ($P < 0.0001$; Fig. 3C and D).

Next, we examined the function of FOXC1 in breast cancer cells. Overexpression of FOXC1 in MDA-MB-231 BLBC cells (harboring moderate levels of endogenous FOXC1) increased cell proliferation, migration, and invasion (Fig. 4A). Similar results were observed in MCF-7 luminal breast cancercells (harboring undetectable levels of endogenous FOXC1; Supplementary Fig. S7A). FOXC1 overexpression also enhanced anchorage-independent growth of MCF-7 cells in soft agar. Immunoblotting indicated that cyclin D1, fibroblast markers (vimentin, fibronectin, and

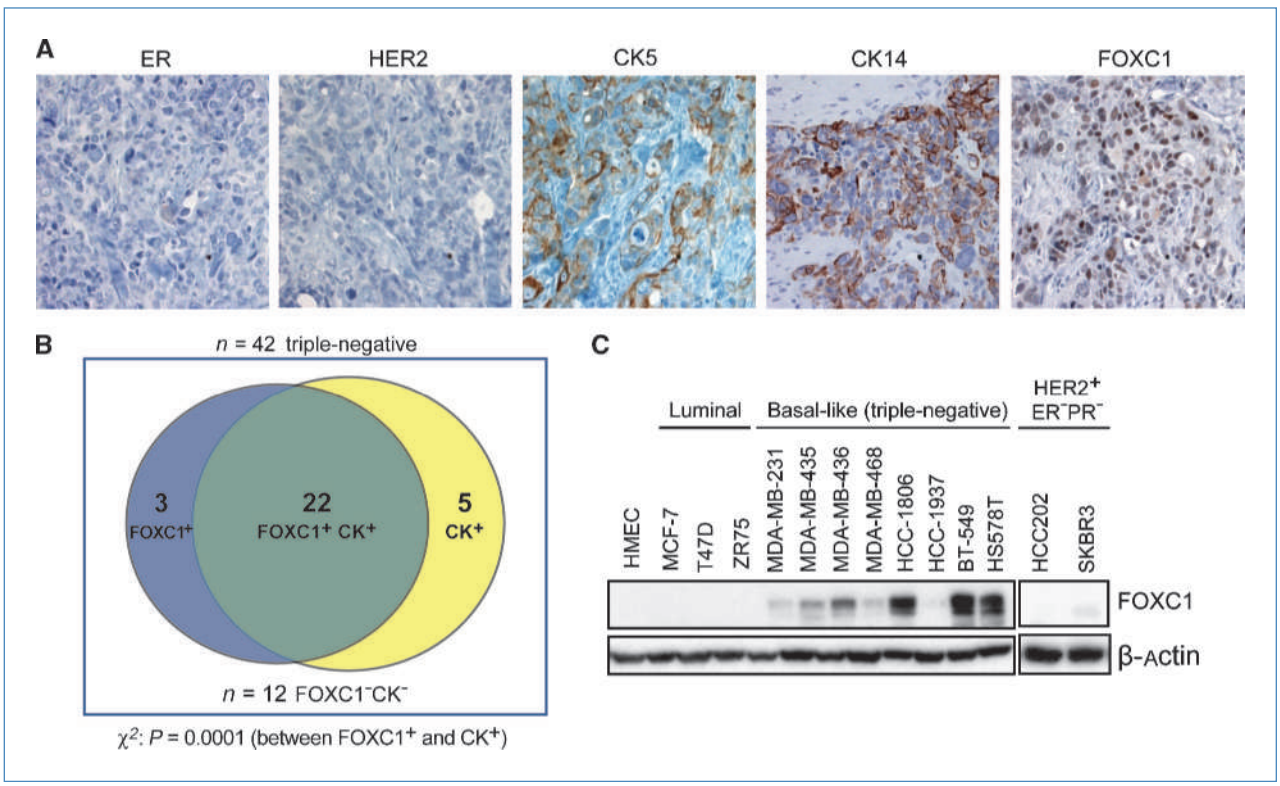

Figure 2. FOXC1 protein expression in BLBC. A, representative immunohistochemical images of a basal-like sample from breast cancer tissue microarrays stained for ER, HER2, CK5/6, CK14, and FOXC1. FOXC1 protein was not detected in non–triple-negative specimens. B, Venn diagram showing the association between FOXC1 and cytokeratin (CK5/6 and/or CK14) immunohistochemistry status in triple-negative tumors. C, immunoblotting of FOXC1 in normal HMECs and luminal (MCF-7, T47D, and ZR75), HER2-overexpressing (SKBR3 and HCC202), or BLBC cell lines.

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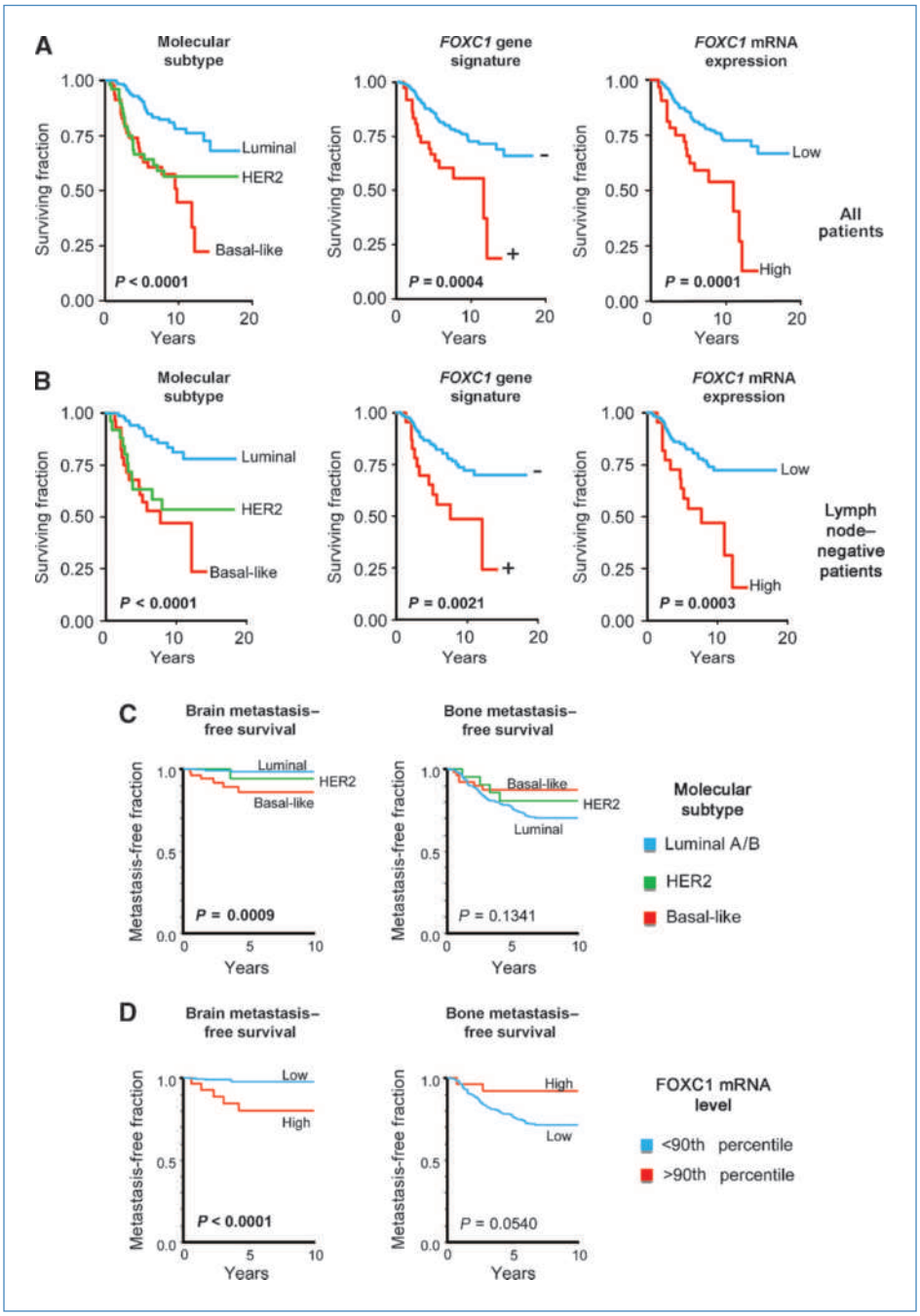

Figure 3. Prognostic significance of FOXC1 in human breast cancer. A, Kaplan-Meier curves of overall survival using data from the van de Vijver et al. data set (14). Overall survival was stratified by molecular subtypes (left), the *FOXC1* gene signature (middle), and FOXC1 mRNA levels (right). B, Kaplan-Meier curves of overall survival in lymph node–negative patients from the same data set. C, Kaplan-Meier curves of brain (left) and bone (right) metastasis–free survival using data from the Wang et al. data set (17) stratified by molecular subtypes. D, Kaplan-Meier curves of brain and bone metastasis–free survival stratified by FOXC1 mRNA levels from the same data set.

α-smooth muscle actin), integrins β_4 and β_1, and matrix metalloproteinases MMP2 and MMP9 were upregulated by FOXC1 overexpression (Supplementary Fig. S7B–D). FOXC1 has been shown to induce epithelial-mesenchymal transition (EMT) in MCF-12A mammary epithelial cells (21). Similarly, FOXC1 overexpression in MCF-10A mammary epithelial cells induced a mesenchymal phenotype accompanied by increased expression of the basal marker P-cadherin and decreased expression of the epithelial marker E-cadherin (Supplementary Fig. S7E). Regulation of these genes by FOXC1 was also confirmed by quantitative reverse transcription-PCR (data not shown). These data suggest that FOXC1 can elicit an aggressive phenotype associated with BLBC cells.

To assess the effects of FOXC1 depletion, we stably transduced FOXC1 shRNA into 4T1 mouse breast cancer cells, which are a model for stage IV human breast cancer (22) and possess high levels of endogenous FOXC1 (Supplementary Fig. S8A). These shRNAs reduced FOXC1 levels by >90% (Supplementary Fig. S8B) and decreased cell

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proliferation, migration, and invasion (Fig. 4B). Similar results were obtained with BT549 human breast cancer cells when FOXC1 was reduced by shRNA (Supplementary Fig. S8C and D). FOXC1 depletion also converted 4T1 cells from fibroblast-like to epithelial-like and suppressed cell growth in three-dimensional culture and colony formation in soft agar (Fig. 4C and D). These data further suggest a role of FOXC1 in regulation of cell function.

Studies have suggested that BLBC may possess extraordinarily high growth rates (23) and an EMT phenotype (24) compared with other breast cancer subgroups. FOXC1 may play a role in coordinating these BLBC properties. The mechanism for exclusive induction of FOXC1 in BLBC is not clear. A recent high-resolution array comparative genomic hybridization analysis revealed that the *FOXC1* gene is not amplified in the basal-like tumors (25). Interestingly, *FOXC1* is one of the genes highly expressed and hypomethylated in $CD44^+CD24^-$ breast cancer cells (21); however, $CD44^+CD24^-$ cells are also present in nonbasal subtypes. Whether DNA methylation plays a dominant role in BLBC-associated FOXC1 expression remains to be determined. The exclusive expression of FOXC1 in BLBC may be due to multiple regulatory mechanisms. In summary, our study suggests that FOXC1 may be a potentially significant diagnostic and prognostic biomarker for BLBC and may serve as a therapeutic target for BLBC.

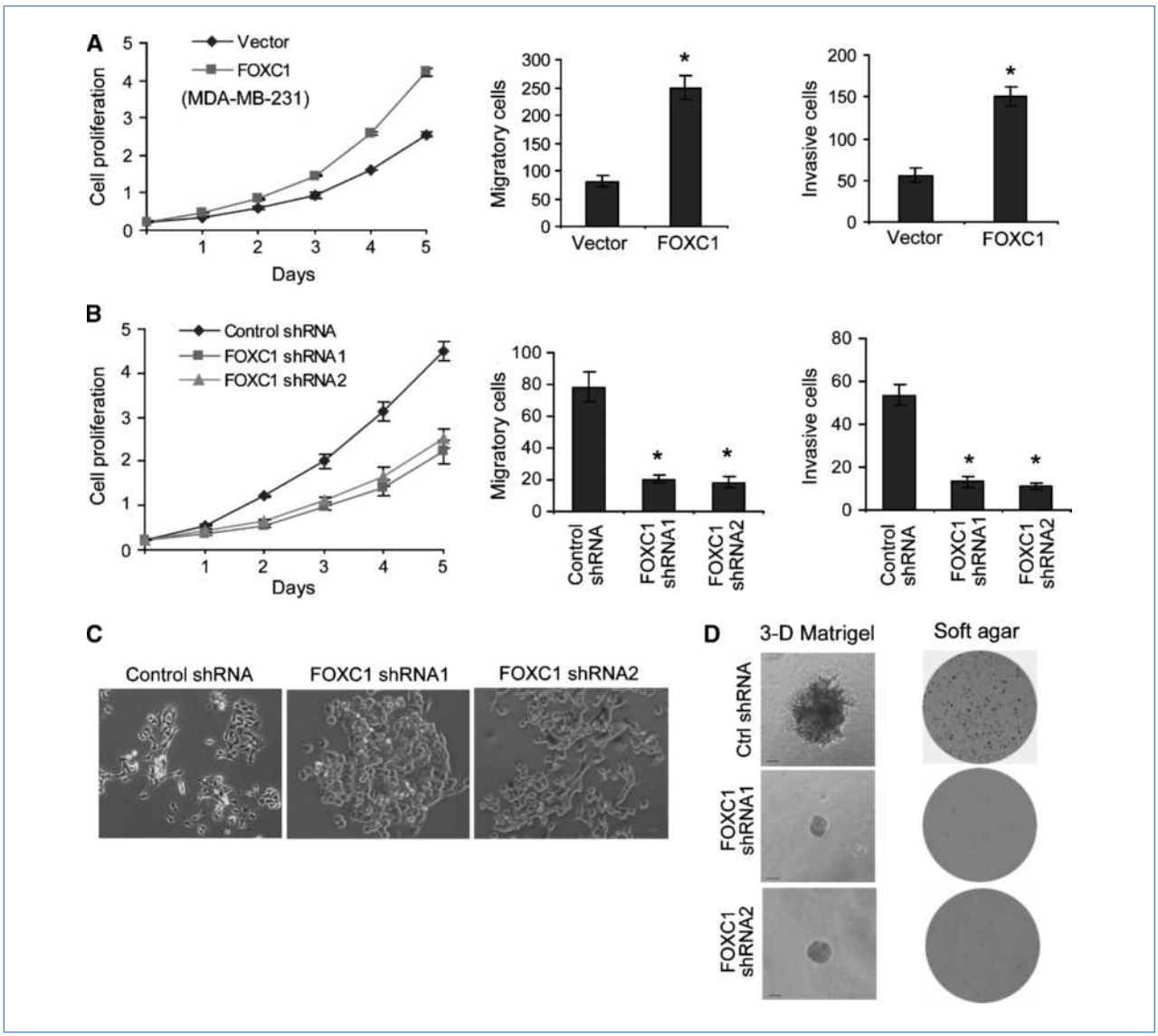

Figure 4. Effects of FOXC1 overexpression and knockdown in breast cancer cells. A, cell proliferation (left), migration (middle), and invasion (right) of FOXC1- or vector-overexpressing MDA-MB-231 cells. Columns, mean ($n = 3$); bars, SD. *, $P < 0.05$, versus the control. B, cell proliferation, migration, and invasion of control or FOXC1 shRNA–expressing 4T1 cells. *, $P < 0.05$, versus the control. C, morphologies of control and FOXC1 shRNA 4T1 cells in monolayer culture. D, representative images of control and FOXC1 shRNA 4T1 cells grown in three-dimensional (3-D) Matrigel (left) and soft agar (right). Bar, 135 μm.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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