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Aberrant Expression of Solute Carrier Family 35 Member A2 Correlates With Tumor Progression in Breast Cancer

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Abstract. *Background/Aim: A recent study suggested that solute carrier family 35 member A2 (SLC35A2) is related to poor prognosis in patients with breast cancer. SLC35A2 transports uridine diphosphate-galactose from the cytosol to the lumen of the endoplasmic reticulum and Golgi. Materials and Methods: Immunohistochemical expression of SLC35A2 was evaluated using tissue microarrays. Cell growth, migration, and invasion of breast cancer cells were examined following loss- and gain-of-expression of SLC35A2. Results: Normal breast tissue exhibited SLC35A2 immunoreactivity in the nucleus. A progressive increase in cytoplasmic expression from in situ carcinoma to invasive carcinoma was observed. There was a correlation between cytoplasmic SLC35A2 expression and breast cancer stage ($p<0.001$). MDA-MB-468 and MCF-7 cells transfected with SLC35A2 shRNA had unchanged cell viability but significantly reduced cell migration and invasion. In contrast, MDA-MB-231 and HCC1806 cells transfected with the SLC35A2 expression vector showed increased migration. Conclusion: Breast cancer progression is accompanied by differential expression patterns of SLC35A2. The migratory or invasive capacity of breast cancer cells is associated with SLC35A2 expression.*

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Solute carrier proteins are the largest group of transporters that control essential physiological functions of cells (1). Among solute carrier proteins, nucleotide sugar transporters, such as the solute carrier family 35 (SLC35), supply substrates for glycosylation (2). Glycosyltransferases that catalyze the transfer of sugar moieties to proteins and lipids are transmembrane proteins with glycosylation reactions occurring in the lumen of the endoplasmic reticulum (ER) or the Golgi apparatus. Nonetheless, the substrates for glycosylation are synthesized either in the cytosol or the nucleus. SLC35 transporters are therefore necessary to transport nucleotide sugars across the lipid bilayer membranes of the ER and Golgi. Currently, the SLC35 family comprises 31 member proteins and is divided into seven subfamilies, from SLC35A to SLC35G (3).

A recent bioinformatics study disclosed that SLC35A2 was substantially related to poor prognosis in patients with breast cancer (4). The human SLC35A2 gene is located on chromosome Xp11.23 and encodes the uridine diphosphate (UDP)-galactose transporter. In the normal human mammary gland, the mRNA expression of SLC35A2 is low (5). Up-regulation of SLC35A2 has been previously reported in colon cancer (6). However, it remains unknown whether breast cancer tissue exhibits differential SLC35A2 protein expression patterns, and the biological roles of SLC35A2 in breast cancer cells are still to be defined. In this study, we investigated SLC35A2 expression in breast tumors using immunohistochemical staining and explored its functional implications through an approach involving loss- and gain-of-expression of SLC35A2 in breast cancer cells.

Materials and Methods

Immunohistochemistry. Two tissue microarrays of breast neoplasms used in this study were obtained from US Biomax Inc., Rockville, MD, USA. The BB08015 set contained 48 tissue cores from 24 patients (ductal carcinoma *in situ*, n=20; invasive ductal carcinoma,

n=4). The BC08118a set contained 100 tissue cores from 100 patients (invasive ductal carcinoma, n=80; invasive lobular carcinoma, n=5; other carcinoma, n=5; normal breast tissue, n=10). The tissue microarray slides were subjected to deparaffinization, rehydration, and antigen retrieval. The slides were then incubated with primary antibody at 1:100 dilution at 4˚C overnight. Rabbit anti-human SLC35A2 polyclonal antibody (catalog number HPA036087) was purchased from Sigma-Aldrich, St. Louis, MO, USA. Diaminobenzidine (DAB) was used for color development and hematoxylin for counterstaining. Negative control slides were included by omitting primary or secondary antibodies. Quantification of SLC35A2 expression was based on the intensity of cytoplasmic immunoreactivity in breast epithelial cells (7). Intensity variation in the staining was semiquantitatively scored as 0, 1+, 2+, and 3+.

Cell cultures. Human breast cancer cell lines MDA-MB-468, MCF-7, MDA-MB-231, and HCC1806 were obtained from the American Type Culture Collection (Manassas, VA, USA). MDA-MB-468 and MDA-MB-231 cells were maintained in Leibovitz's L-15 Medium supplemented with 10% fetal bovine serum (FBS). MCF-7 cells were grown in Eagle's Minimum Essential Medium supplemented with 10% FBS, whereas HCC1806 cells were grown in RPMI-1640 Medium supplemented with 10% FBS. All cell lines were maintained at 37˚C in a humidified atmosphere with 5% CO2. Cells were authenticated using short tandem repeat analyses and tested for mycoplasma contamination.

Transfection. For knockdown experiments, shRNA constructs in a lentiviral green fluorescent protein (GFP) vector (catalog number TL309328) were purchased from OriGene Technologies (Rockville, MD, USA). MDA-MB-468 and MCF-7 cells were transfected with a control shRNA or shRNA against SLC35A2 using Lipofectamine 3000 Reagent (Thermo Fisher Scientific, Waltham, MA, USA) and selected with puromycin. For over-expression experiments, a CMV promoter-driven over-expression vector (catalog number EX-X0168-M46) was purchased from GeneCopoeia, Rockville, MD, USA. MDA-MB-231 and HCC1806 cells were transfected with an empty vector or SLC35A2-expression vector using Lipofectamine 3000 Reagent and selected with G418. Transfection efficiency was evaluated using fluorescence microscopy for GFP detection. Knockdown efficacy was confirmed by immunoblotting.

Western blot analysis. Proteins extracted from whole cell lysates were subjected to electrophoresis on a 12% polyacrylamide gel followed by transfer to a polyvinylidene difluoride membrane (8). The membrane was blocked in 5% skim milk for 1 h and then incubated with a primary antibody against SLC35A2 (1:3,000 dilution; catalog number ab222854; Abcam, Cambridge, UK) at 4˚C overnight. α-Tubulin (catalog number T5168; Sigma-Aldrich) or GAPDH (catalog number ab9485; Abcam) was used as a loading control.

Cell viability. A colorimetric CellTiter Aqueous One Solution Cell Proliferation (MTS) Assay (Promega, Madison, WI, USA) was used to measure the effect of modulation of SLC35A2 expression on the viability of human breast cancer cells (9). Stably transfected breast cancer cells were grown in 96-well plates. After 24 to 96 h, the MTS reagent was added to the washed cells and incubated for 120 min at 37˚C before absorbance at 490 nm was measured.

Transwell assay. Transwell assays were carried out using modified Boyden chambers as previously described (10). Stably transfected breast cancer cells were seeded in serum-free medium onto the Transwell insert with 8.0 μm-pore polycarbonate membrane (catalog number 3422; Corning Life Sciences, Tewksbury, MA, USA). For the invasion assay, we used a chamber in which the inserts were pre-coated with the extracellular matrix Matrigel (catalog number 354480; Corning Life Sciences). The cells that migrated or invaded through the insert membrane were stained with Diff-Quik (Sysmex, Kobe, Japan) and counted under a microscope.

Statistical analysis. The relationship between immunohistochemical SLC35A2 expression and tumor stage was determined using the Cochran-Armitage trend test (11). Otherwise, data from three or more independent experiments were compared using an unpaired Student's *t*-test or analysis of variance. A two-sided *p*-value <0.05 was considered statistically significant.

Results

Expression of SLC35A2 in breast neoplasms. We performed immunohistochemical staining in two commercial tissue microarrays to evaluate the expression of SLC35A2 in breast neoplasms. As shown in Figure 1A, normal breast tissue exhibited SLC35A2 immunoreactivity in the nucleus. There was undetectable or faint SLC35A2 immunoreactivity in the cytoplasm. For ductal carcinoma *in situ*, a wane in nuclear SLC35A2 expression was noted. In situ proliferation was accompanied by heterogenous, mild to moderate cytoplasmic SLC35A2 immunoreactivity. For invasive ductal or lobular carcinoma, a coarsely granular pattern with perinuclear accentuation was observed. In a minority of samples, diffuse homogeneous cytoplasmic staining was present. Altogether, differential SLC35A2 expression patterns were associated with malignant transformation of the breast epithelium.

Significance of SLC35A2 expression. We quantified cytoplasmic SLC35A2 expression in a total of 84 female patients with invasive ductal carcinoma. Mild (1+), moderate (2+), and strong (3+) cytoplasmic staining were present in 21 (25%), 36 (43%), and 27 (32%) patients, respectively. Interestingly, we observed a positive association between SLC35A2 expression and tumor-node-metastasis stage ($p<0.001$, Figure 1B). Furthermore, SLC35A2 expression was positively associated with patient age ($p=0.001$). There was no association between SLC35A2 expression and tumor grade ($p=0.110$). Collectively, cytoplasmic over-expression of SLC35A2 in breast cancer was parallel to tumor progression.

Effects of SLC35A2 modulation on cell viability. Based on our preliminary screening, MDA-MB-468 and MCF-7 cells had relatively high SLC35A2 expression, while the expression of SLC35A2 in MDA-MB-231 and HCC1806 cells was relatively low. Accordingly, MDA-MB-468 and MCF-7 cells were transfected with SLC35A2 shRNA to

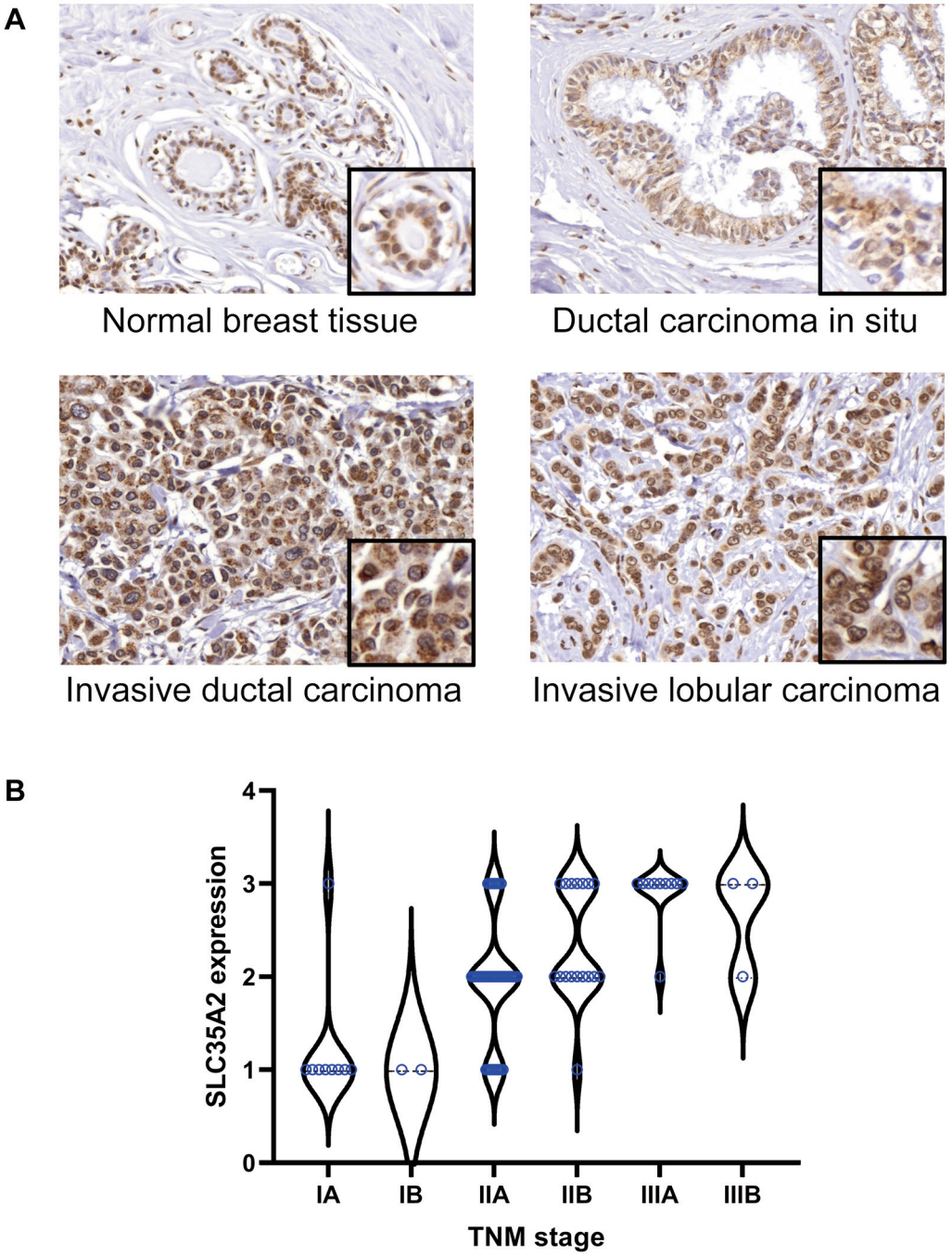

Figure 1. *Immunohistochemical expression of SLC35A2 in breast cancer neoplasms. (A) Representative microphotographs of immunohistochemical staining of SLC35A2 in normal breast tissue, ductal carcinoma in situ, invasive ductal carcinoma, and invasive lobular carcinoma. Original magnification, ×200; inset, ×400. (B) A violin plot shows the association between SLC35A2 expression and tumor-node-metastasis (TNM) stage in 84 patients with invasive ductal carcinoma.*

knockdown SLC35A2 expression, and MDA-MB-231 and HCC1806 cells were transfected with the SLC35A2 expression vector to enhance SLC35A2 expression (Figure 2A). Nonetheless, knockdown of SLC35A2 expression did not influence cell growth in MDA-MB-468 and MCF-7 cells (Figure 2B). Similarly, over-expression of SLC35A2 in MDA-MB-231 and HCC1806 cells had no effect on cell viability (data not shown).

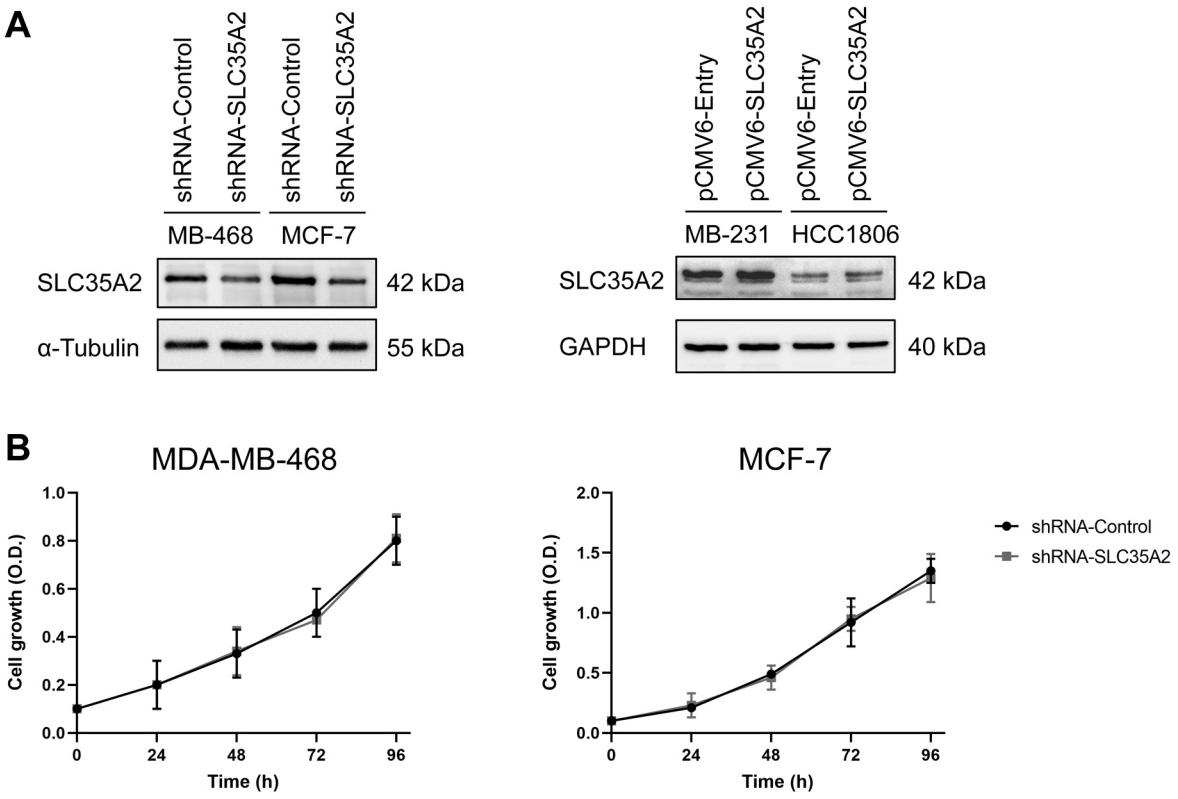

Figure 2. *Modulation of SLC35A2 expression in breast cancer cells and its effect on cell growth. (A) Human breast cancer cell lines MDA-MB-468 and MCF-7 were transfected with a control shRNA or shRNA against SLC35A2, while MDA-MB-231 and HCC1806 were transfected with an empty vector or SLC35A2-expression vector. The expression of SLC35A2 was evaluated using immunoblotting. (B) Cell growth was determined by the CellTiter Aqueous One Solution Cell Proliferation (MTS) assay.*

Effects of SLC35A2 modulation on cell migration and invasion. We conducted Transwell assays to evaluate the effects of SLC35A2 up-regulation or down-regulation on the migratory or invasive capacity of breast cancer cells. Of interest, knockdown of SLC35A2 expression significantly reduced cell migration and invasion in MDA-MB-468 and MCF-7 cells (Figure 3). Conversely, SLC35A2 over-expression had the opposite effect. Over-expression of SLC35A2 significantly increased the migratory ability of MDA-MB-231 and HCC1806 cells (Figure 4A). Invasive ability also tended to increase following SLC35A2 over-expression, but the difference did not reach statistical significance (Figure 4B). Taken together, experimental evidence suggests a linkage between SLC35A2 expression and the migratory and invasive capacity of breast cancer cells.

Discussion

We observed an over-expression of cytoplasmic SLC35A2 in breast malignancies compared to normal breast tissue. Additionally, there was an increase in expression levels from *in situ* carcinoma to invasive carcinoma, and a strong positive relationship between SLC35A2 expression and disease stage was noteworthy. In agreement with our findings, a study showed that the top five protein-coding genes closely correlated to the poor prognosis of breast cancer were SLC35A2, QPRT, CD24, DCTPP1, and CCDC24 (12). Our in-house analysis of The Cancer Genome Atlas (TCGA) data revealed that the HER2-enriched subtype had the highest SLC35A2 expression, while luminal A and normal-like subtypes had the lowest SLC35A2 expression. However, information regarding the status of hormonal receptors and HER2 was unavailable for patients included in the tissue microarrays of the current study.

SLC35A2 encodes the X-linked transporter that carries UDP-galactose from the cytosol to the lumen of the ER and Golgi apparatus. It is so far the only known transporter of UDP-galactose in mammals, and mutations in the SLC35A2 gene have been linked to SLC35A2-congenital disorders of glycosylation (CDG) (13). However, an alternative UDP-galactose transporter has been proposed (14). The role of SLC transporters in cancer research is emerging as a new field of investigation. A recent CRISPR-Cas9 screening

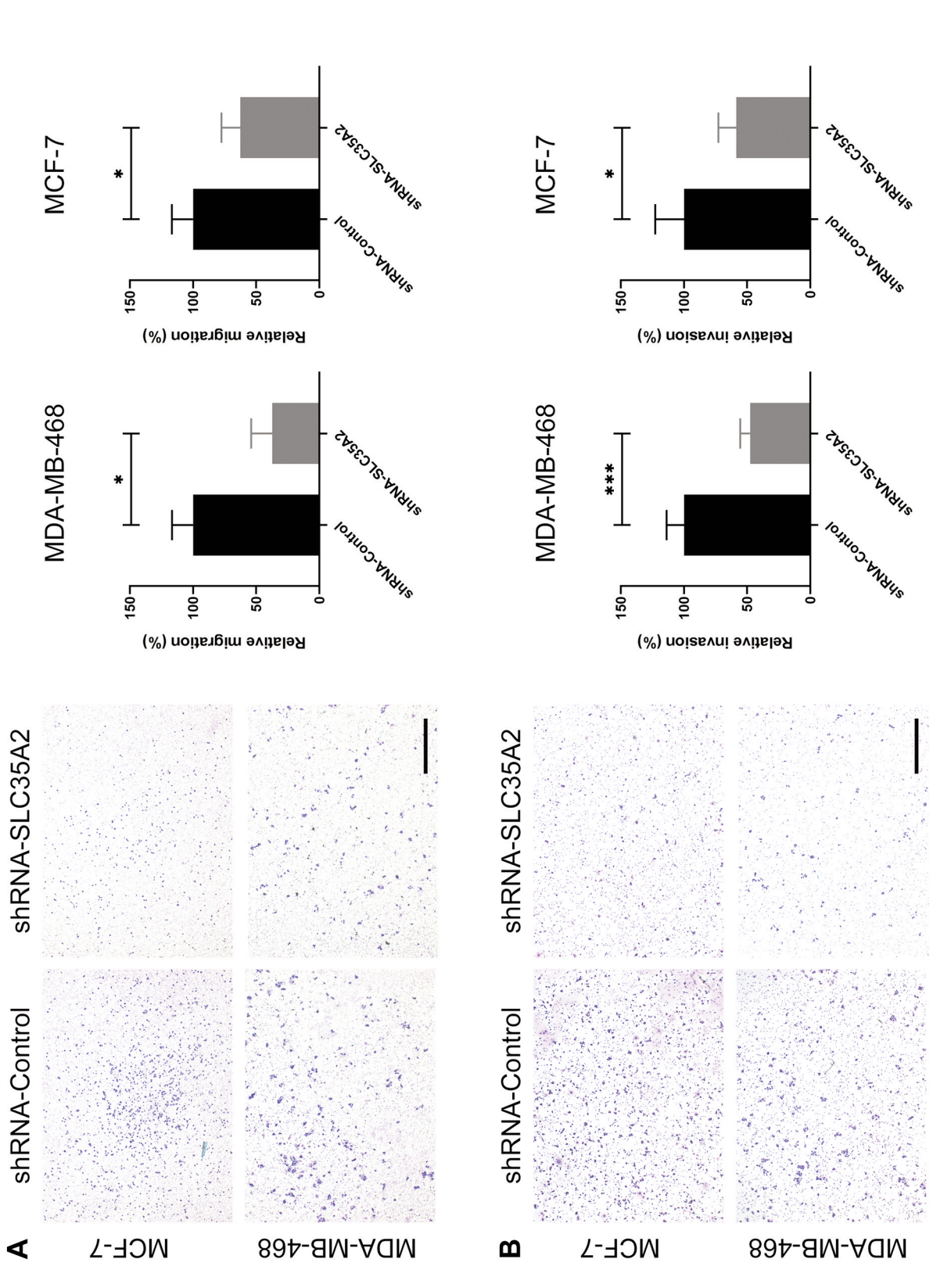

Figure 3. *Effects of SLC35A2 knockdown on cell migration and invasion in breast cancer cells. Human breast cancer cell lines MDA-MB-468 and MCF-7 were transfected with a control shRNA or shRNA against SLC35A2. Migration (A) and invasion (B) assays were performed in Transwell chambers either without or with the Matrigel coating. Scale bars, 500 μm. *p<0.05; ***p<0.001.*

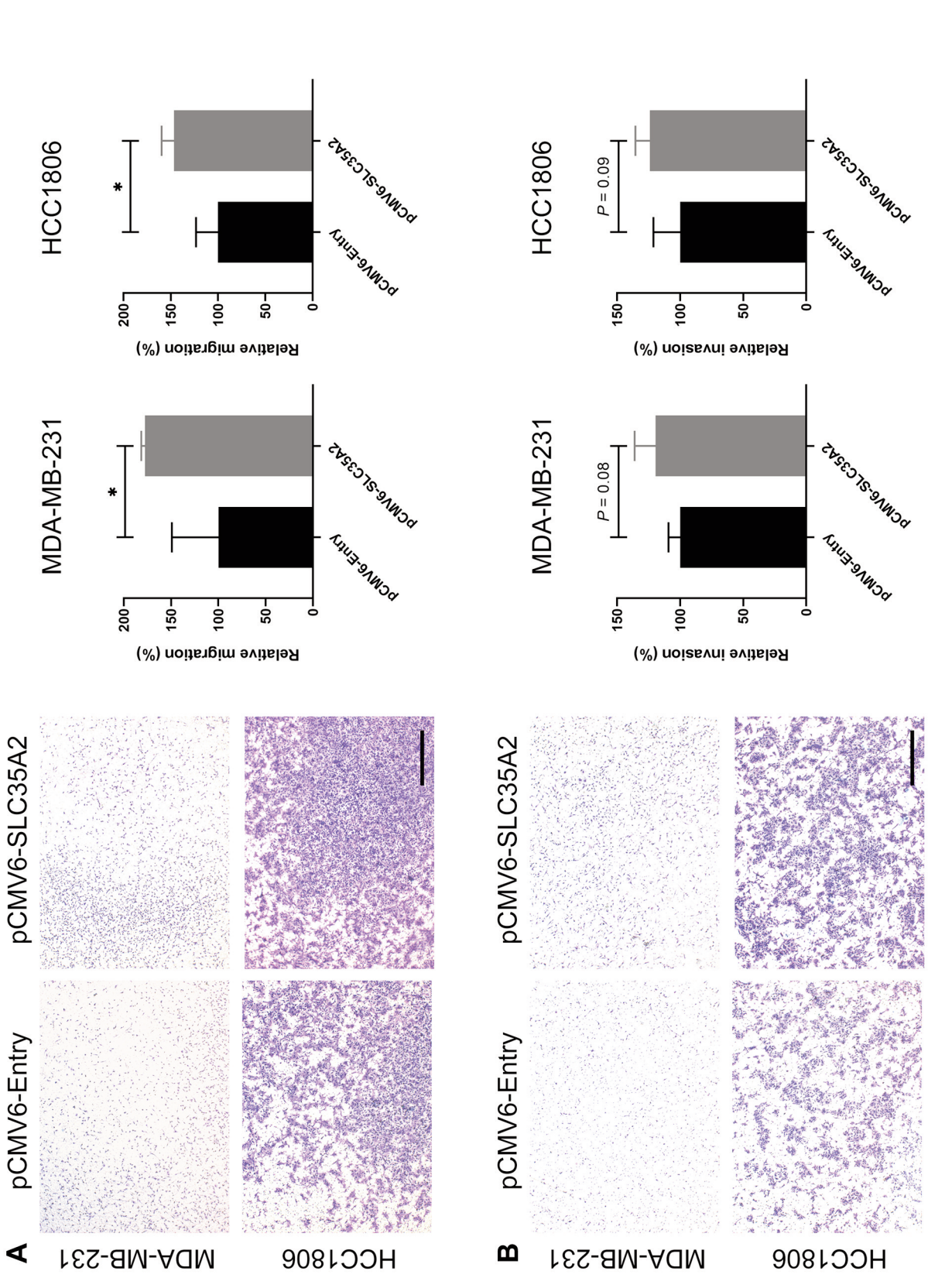

Figure 4. *Effects of SLC35A2 over-expression on cell migration and invasion in breast cancer cells. Human breast cancer cell lines MDA-MB-231 and HCC1806 were transfected with an empty vector or SLC35A2-expression vector. Migration (A) and invasion (B) assays were performed in Transwell chambers either without or with the Matrigel coating. Scale bars, 500 μm. *p<0.05.*

identified an increased resistance to the DNA-damaging agent cisplatin in the SLC35A2-deficient cells (15). MetaCore pathway analysis of SLC35A2 co-expressed genes suggests that SLC35A2 may play a role in cell cycle regulation (4). Nonetheless, we found that cell growth was not affected by modulation of SLC35A2 expression in the present study. The interaction between SLC35A2 expression and the DNA damage response deserves further study.

Our loss- and gain-of-expression studies suggest that SLC35A2 participates in cell migration and invasion in breast cancer cells. Invasion of adjacent tissue and seeding at distant sites to form metastases are the hallmark of cancer and the leading causes of cancer deaths (16). Consistent with our findings, a previous study found that up-regulation of SLC35A2 in colon cancer was frequently observed in patients with lymph node or distant metastasis (6). The study showed that the expression of sialyl Lewis A and sialyl Lewis X determinants was significantly induced by transfection with SLC35A2, which led to an enhanced adhesion of cancer cells to vascular E-selectin (6). In breast cancer, galactosylceramide and galactosyltransferase, an enzyme responsible for the synthesis of galactosylceramide, have a profound effect on tumorigenic and metastatic properties (17). Given that SLC35A2 is involved in the synthesis of galactosylceramide in the ER (3), it is possible that SLC35A2 promotes metastatic spread of breast cancer cells through multiple downstream molecules.

The underlying mechanisms resulting in aberrant expression of SLC35A2 during breast tumor progression are still unknown. In colon cancer, hypoxia induced robust expression of SLC35A2 and other adhesion molecules (18). We analyzed the TCGA data and corroborated a moderate, positive relationship between the expression of SLC35A2 and hypoxia inducible factor-1α. Hypoxia is a well-known regulator of cancer progression and metastasis (19). It is tempting to investigate whether differential SLC35A2 expression in breast cancer is related to the hypoxic tumor microenvironment and whether breast cancer progression can be hindered by targeting SLC35A2 activity or expression.

In conclusion, differential expression patterns of SLC35A2 were observed during breast cancer development and progression. We found that SLC35A2 expression in breast cancer cells is associated with an increased ability to migrate and invade. SLC35A2 may represent a prognostic biomarker and therapeutic target in the management of patients with breast cancer.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Liu CL, Cheng SP, and Chang YC conceived the study, designed, and performed experiments, analyzed data, and wrote the manuscript. Huang WC, Chen MJ, and Lin CH provided technical support and conceptual advice. Chen SN assisted in carrying out the experiments. All Authors read the manuscript and approved the final version.

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