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Estrogen induced β-1,4-galactosyltransferase 1 expression regulates proliferation of human breast cancer MCF-7 cells

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ABSTRACT

Beta 1,4-galactosyltransferase 1 (B4GALT1) synthesizes galactose β-1,4-*N*-acetylglucosamine (Galβ1-4GlcNAc) groups on *N*-linked sugar chains of glycoproteins, which play important roles in many biological events, including the proliferation and migration of cancer cells. A previous microarray study reported that this gene is expressed by estrogen treatment in breast cancer. In this study, we examined the regulatory mechanisms and biological functions of estrogen-induced B4GALT1 expression. Our data showed that estrogen-induced expression of B4GALT1 is localized in intracellular compartments and in the plasma membrane. In addition, B4GALT1 has an enzyme activity involved in the production of the Galβ1-4GlcNAc structure. The result from a promoter assay and chromatin immunoprecipitation revealed that 3 different estrogen response elements (EREs) in the *B4GALT1* promoter are critical for responsiveness to estrogen. In addition, the estrogen antagonists ICI 182,780 and ER-α-ERE binding blocker TPBM inhibit the expression of estrogen-induced B4GALT1. However, the inhibition of signal molecules relating to the extra-nuclear pathway, including the G-protein coupled receptors, Ras, and mitogen-activated protein kinases, had no inhibitory effects on B4GALT1 expression. The knock-down of the *B4GALT1* gene and the inhibition of membrane B4GALT1 function resulted in the significant inhibition of estrogen-induced proliferation of MCF-7 cells. Considering these results, we propose that estrogen regulates the expression of B4GALT1 through the direct binding of ER-α to ERE and that the expressed B4GALT1 plays a crucial role in the proliferation of MCF-7 cells through its activity as a membrane receptor.

1. Introduction

The biosynthesis of complex glycans is strictly controlled by various subsets of specific enzymes known as the glycosyltransferases [1]. Among these glycosyltransferases, β-1,4-galactosyltransferase 1 (B4GALT1) is one of the key enzymes involved in the synthesis of the Galβ1-4GlcNAc groups in *N*-glycan and core-2 *O*-glycans of glycolproteins [2]. B4GALT1 is a type II membrane-bound glycoprotein, existing in 2 distinct subcellular compartments, the trans-Golgi network and on the plasma membrane [3]. The majority of the B4GALT1 act as galactosyltranferases in the Golgi apparatus; in contrast, a small portion of the B4GALT1 works as receptors for the recognition of specific ligands [3,4]. As a result, the B4GALT1 play a variety of roles in physiological and pathological conditions, such as neurite extension [5], sperm–egg interaction [6], and metastasis and proliferation of cancer [7,8].

Since the promoter region upstream of the B4GALT1 start site contains the ubiquitous transcription factor Sp1, it has long been considered as a housekeeping gene [9]. However, there is accumulating evidence suggesting that the expression of B4GALT1 is enhanced by its inflammatory status, which is induced by lipopolysaccharide (LPS) stimulation [10], tumor necrosis factor-α (TNF-α) treatment [11], and nerve injury [12]. In addition, B4GALT1 expression is related to cell cycle [7], apoptosis [13], and metastasis [14] of cancer cells. Recently, Villegas-Comonfort et al. [15] reported that arachidonic acid (AA) increased the expression of B4GALT1 and subsequent cellular adhesion in MDA-MB-231 breast cancer cells.

Estrogen is an important regulator in the development and progression of breast cancers [16]. The biological effects of estrogen are mediated through 2 distinct signaling pathways: the direct binding of the estrogen receptor (ER) to the estrogen responsive element (ERE) in the promoter region of the target gene, and the extra-nuclear function of the ER in the cytoplasm and plasma

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membrane [17]. Estrogen is important for the production of *N*-linked glycoproteins through regulation of the glycosyltransferases, including mannosyl phosphoryldolichol synthase [18], fucosyltransferases [19], and sialyltransferase [20]. Using cDNA microarray analysis, Wang et al. [21] reported that B4GALT1 expression is responsive to estrogen in breast cancer cells.

However, the biological functions and signaling pathways underlying estrogen-induced expression of B4GALT1 have not been fully elucidated. In this study, we found that estrogen-induced B4GALT1 expression is regulated by a direct nuclear pathway, and not by indirect extra-nuclear signaling pathways. In addition, B4GALT1 expression plays a key role in the regulation of MCF-7 cell proliferation.

2. Materials and methods

2.1. Materials

Antibodies against B4GALT1 (N-term and C-term), ER-α, epidermal growth factor receptor (EGFR), lamin B, p65 subunit of NF-κB and β-actin were all purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Cell culture reagents were purchased from Gibco-BRL (Rockville, MD). All the other chemicals and reagents were obtained from Sigma–Aldrich (St. Louis, MO), unless otherwise indicated.

2.2. Cell culture

MCF-7 cells were obtained from the ATCC (American Type Culture Collection, Rockville, MD) and grown in Dulbecco's Modified Eagle's Medium (DMEM) containing L-glutamine (200 mg/L) (Gibco-BRL) supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS; Sigma–Aldrich), and 100 U/mL penicillin and 100 μg/mL streptomycin in a humidified incubator with 37 °C, 5% CO_2 prior to experimentation. To avoid the influence of lipid hormones, FBS was incubated overnight at 4 °C with 20 g/L dextran-coated charcoal (DCC; Sigma–Aldrich).

2.3. Confocal microscopic observation

MCF-7 cells maintained on glass coverslips were transfected with or without siGalT for 24 h and subsequently stimulated with estrogen. After 24 h, the cells were fixed with 4% paraformaldehyde in PBS, and permeabilized with 0.2% Triton X-100 in PBS. For the detection of proteins on the outer membrane, the permeabilizing process was omitted. After 1 h incubation with blocking buffer (5% BSA in PBS), the cells were incubated with anti-B4GALT1 antibody (1:1000) for 1 h, followed by 1 h of incubation with fluorescein isothiocyanate (FITC)-conjugated anti-mouse IgG antibody (1:400; Invitrogen, Carlsbad, CA). After washing with cold PBS, cells were mounted on glass slides using VECTASHIELD Mounting Medium with DAPI (Vector Lab., Burlingame, CA). Fluorescent images were obtained using a ZEISS LSM700 laser scanning confocal microscope (Carl Zeiss, Oberkochen, Germany).

2.4. Detection of Galβ1-4GlcNAc by fluorescence-activated cell sorter (FACS) analysis

MCF-7 cells were grown in a medium containing DCC-FBS for 24 h and then treated with E2 (10 nm) for 24 h. The cells were harvested and a single cell suspension (1×10^6) was subsequently incubated with biotinylated *Ricinus communis* agglutinin-120 (RCA-120; Vector Lab.), followed by treatment with FITC-conjugated streptavidin-Alexa Fluor 488 (Invitrogen). After incubation, the samples were analyzed by flow cytometry (FACS Canto II; BD Biosciences, Franklin Lakes, NJ).

2.5. Luciferase promoter assay

MCF-7 cells were seeded into 24-well plates (5×10^5 cells/well) and allowed to grow to 50–70% confluence. The plasmids containing different type of B4GALT1 promoter were cotransfected with a pCMV-β-galactosidase reporter plasmid (Promega, Fitchburg, WI). The construction of each plasmid is described in the Supplementary Methods section. The cells were cultured for 24 h with DCC-FBS and then stimulated with E2 (10 nm) for 6 h. The cells were then collected and disrupted *via* sonication in lysis buffer (25 mM Tris–phosphate, pH 7.8, 2 mM EDTA, 1% Triton X-100, and 10% glycerol), and then the cell lysates were assayed for luciferase activity with a luciferase assay kit (Promega). Luciferase activity was normalized against β-galactosidase control activity in the cell lysate.

2.6. Chromatin immunoprecipitation (ChIP) assay

Chromatin immunoprecipitation was performed as outlined by the ChIP assay kit (Upstate, Utica, NY). DNA-binding proteins were crosslinked to DNA and lyzed in SDS lysis buffer containing 1 × protease inhibitors. DNA was sheared to 200–500 bp fragments through 30 s sonication pulses by using a VC100 sonicator (Sonics & Materials Inc., Newtown, CT). The chromatin solution was precleared with salmon DNA/protein A agarose 50% slurry (Upstate) for 30 min at 4 °C. The precleared supernatant was incubated overnight at 4 °C with anti-ER-α antibody and isotypic IgG (Santa Cruz). Precipitated DNA and input genomic DNA was amplified by PCR with the 3 different set of primers shown in Supplementary Table 3. The PCR products were separated on a 2% agarose gel and visualized under UV light.

2.7. Cell proliferation assay

MCF-7 cells were plated in 6-well culture plates at a density of 1×10^6 cells per well in DMEM culture medium supplemented with DCC-incubated FBS (DCC-FBS) and cultured for 24 h. The cells were treated with or without E2 (10 nm), small interfering RNAs, and specific antibodies. After 72 h, the cell number were counted by using the Countess Automated Cell Counter (Invitrogen) according to the manufacturer's instructions.

2.8. Analysis of DNA content by FACS

MCF-7 cells (2×10^6 cells) were centrifuged (2500×*g*, 4 °C, 10 min) and washed twice in PBS buffer. The pellet was gently resuspended in 100 μL PBS, and 200 μL PBS containing 10% ethanol/5% glycerol was then added, followed by 200 μL PBS containing 50% ethanol/5% glycerol; the samples were then incubated on ice for 5 min. A total of 1 mL of PBS containing 70% ethanol/5% glycerol was added to the cell suspension and left at 4 °C overnight, washed with PBS, and resuspended with 12.5 μg of RNase (Sigma–Aldrich) in 250 μL of 1.12% sodium citrate buffer (pH 8.45). Incubation was continued at 37 °C for 30 min before staining the cellular DNA with 250 μL of propidium iodide (50 μg/mL) for 30 min at room temperature. The stained cells were analyzed on a flow cytometer to assess the relative DNA content.

3. Results and discussion

3.1. Estrogen-induced B4GALT1 is localized in both intracellular compartments and on the cell surface

There is a controversial issue concerning the size and localization of the B4GALT1 proteins. Youakim et al. [3] showed that the

long-form B4GALT1 protein localized on the plasma membrane and in the Golgi complex, whereas the short-form B4GALT1 localized only in the Golgi complex [22]. Our result showed that estrogen induced both the long-form and total B4GALT1 expression (Fig. 1A). Because B4GALT1 mRNA transcripts have only 39 bp differences between the short-form and the long-form [4], we were unable to distinguish the short-form B4GALT1 expression from the long-form one by performing RT-PCR. Using Western Blot analysis, we found one specific band corresponding to B4GALT1. The expression of B4GALT1 is increased in a dose-dependent fashion by E2 treatment in the total and membrane fractions of MCF-7 cells (Fig. 1B). In contrast, B4GALT1 was hardly detected in the soluble fraction (data not shown). Based on these results, we assumed that estrogen-induced B4GALT1 expression was mainly the long-form expression.

To elucidate the intracellular localization of B4GALT1, we performed confocal microscopy by using 2 different methods. The results showed that both the intracellular and cell surface B4GALT1 expressions increased on estrogen treatment. The amount of plasma membrane B4GALT1 expression is very small compared with the total B4GALT1 expression (Fig. 1C). It is reported that long-form B4GALT1, which is localized in the trans-Golgi structures and on the plasma membrane, can act as a membrane receptor for specific ligands [19,22]. We next examined the enzymatic action of B4GALT1 by indirectly estimating the expression of Galβ1-4GlcNAc on the cell surface. Using biotinylated RCA120 lectin-based FACS analysis, we observed that the quantity of the cell surface Galβ1-4GlcNAc structures increased by estrogen treatment (Fig. 2C). Thus, we postulated that estrogen-induced B4GALT1 expression acts not only as a membrane receptor but also as a trans-Golgi enzyme.

3.2. Estrogen regulates B4GALT1 expression through the direct binding of ER-α to the ERE site

To reveal the precise mechanism underlying estrogen-induced B4GALT1 expression, we performed a promoter assay by using plasmids harboring different mutants of the B4GALT1 promoter. The luciferase activity was the highest when assayed with a vector harboring approximately 0.5 kb of the 5′-untranslation region upstream of the B4GALT1 gene (Fig. 2A). Within the region of the most potent vector, we found 3 different candidates for the ERE site (Fig. 2C). Using site-direct mutant clones of 3 ERE sites, the luciferase assay showed that each mutant diminished the promoter activity enhanced by estrogen treatment. The ERE-3 site, located in proximity to the transcription start site, is the most potent for promoter activity (Fig. 2B). In agreement with the data from the promoter assay, the results from the ChIP assay showed that each ERE site is responsible for estrogen-induced B4GALT1 expression (Fig. 2D).

We next examined the upstream signaling pathway responsible for estrogen-induced B4GALT1 expression. Estrogen activates various molecular signaling pathways in the cells through binding to the ERs [16]. Classically, the ERs function in the nucleus as ligand-activated transcription factors [23]. Additionally, the ERs can also regulate gene expression in the absence of estrogen following phosphorylation through growth factor signaling pathways [24]. Furthermore, the binding of estrogen with a subpopulation of membrane-associated ERs and G-protein coupled receptors (GPCRs) induces the activation of signaling pathways, including Ras-Raf, the mitogen-activated kinases (MAPKs), phosphatidylinositol 3-kinase, and Akt [17,25]. Our results showed that estrogen induced the nuclear translocation of ER-α but not NF-κB

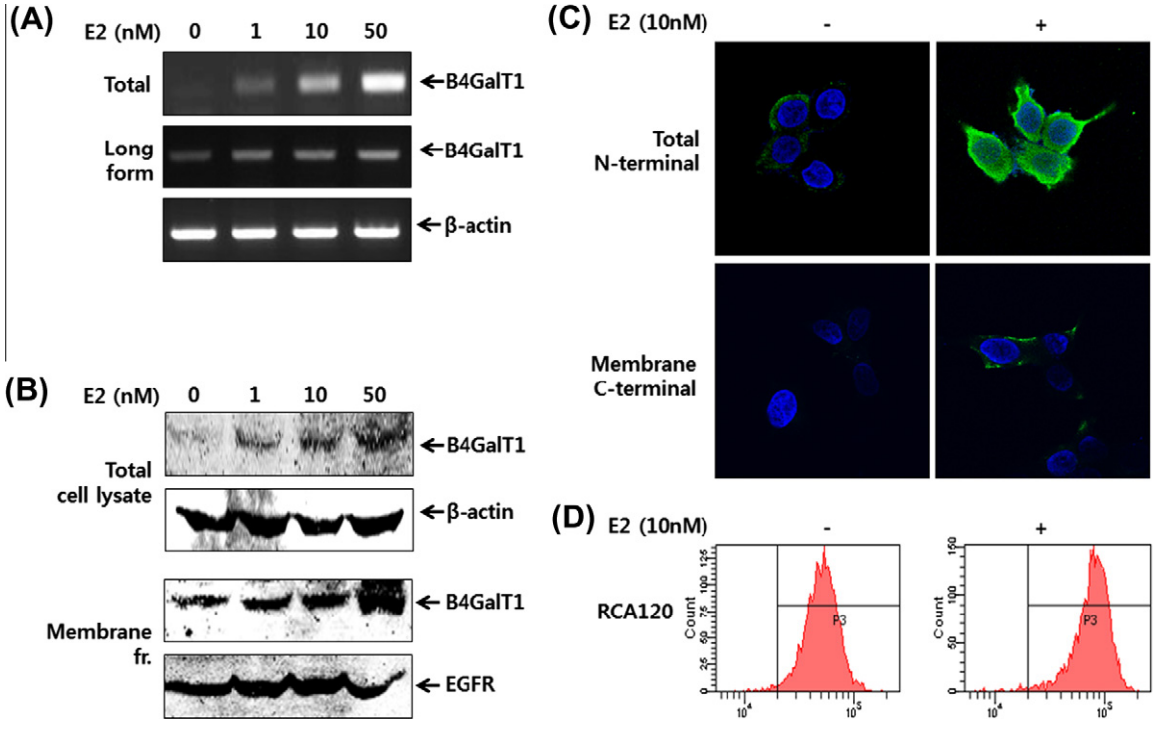

Fig. 1. Estrogen-induced expression of B4GALT1 and its intracellular localization in MCF-7 cells. (A) MCF-7 cells were grown in a medium containing DCC-FBS for 24 h and then treated with the indicated concentration of E2 for 24 h. The expression of B4GALT1 was estimated by performing RT-PCR and Western Blot analysis. (B) The expression of B4GALT1 proteins was estimated by performing Western Blot analysis using the soluble and membrane fractions of the cell lysates. (C) The localization of B4GALT1 proteins (green) was observed by confocal microscopy (×400). For the detection of total B4GALT1, the cells were permeabilized and incubated with an anti-B4GALT1 antibody, specific for N-terminal B4GALT1, and FITC-conjugated secondary antibodies. For detecting cell surface B4GALT1, the cells were not permeabilized and were instead incubated with a C-terminal specific antibody. Nuclei were stained with DAPI (blue). (D) The enzyme activity of B4GALT1 was indirectly measured by detecting Galβ1-4GlcNAc structures on cell surface oligosaccharides using FACS analysis with biotinylated RCA120 lectin and FITC-conjugated streptavidin. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

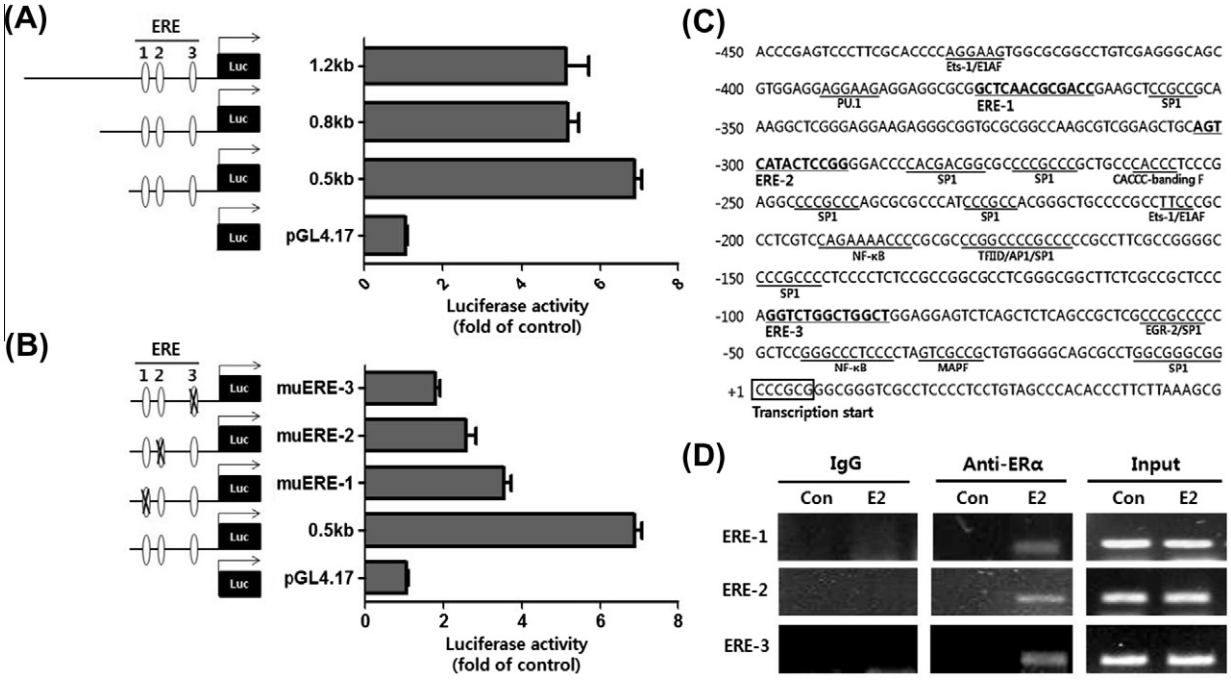

Fig. 2. Identification of 3 different EREs in the B4GALT1 gene promoter. (A and B) MCF-7 cells were cultured with a medium containing DCC-FBS for 24 h and subsequently cotransfected with a plasmid harboring different forms of the B4GALT1 promoter and pCMV-β-galactosidase reporter plasmids. After 24 h, the cells were harvested and a luciferase assay was performed. (C) The sequence 450 bp upstream to 50 bp downstream of the human B4GALT1 transcription site (+1) was represented. Potential transcription factor binding sites, identified by searching the TRANSFAC database, are underlined and labeled. Three different potential estrogen responsive elements (EREs) are indicated in red. (D) MCF-7 cells were treated with E2 (10 nm) for 6 h and the cell lysates were then used for the ChIP assay. DNA bound to ER-α was precipitated with an anti-ER-α antibody. An isotypic IgG was used for the exclusion of nonspecific immunoprecipitation. Precipitated DNA and input genomic DNA were amplified by PCR by using 3 different set of primers listed in Supplementary Table 3.

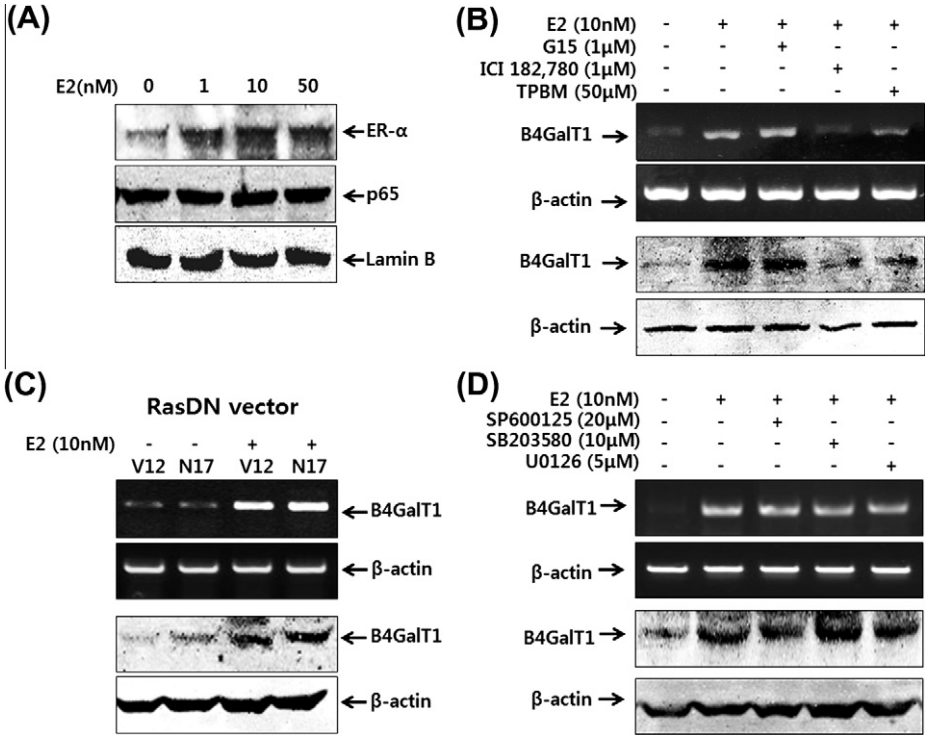

Fig. 3. Identification of a signaling pathway involved in estrogen-induced B4GALT1 expression. (A) MCF-7 cells, supplemented with DCC-FBS for 24 h, were treated with an indicated concentration of E2. The nuclear localization of the ER-α and p65 subunits of NF-κB was detected by Western Blot analysis. (B) MCF-7 cells were grown in a medium containing DCC-FBS for 24 h. Cells were pretreated with inhibitors, such as G15 (1 μM), ICI 182,780 (1 μM), and TPBM (50 μM), 30 min before E2 (10 nm) treatment. After 24 h, the cells were harvested and the expression of B4GALT1 was estimated by performing RT-PCR and Western Blot analysis. (C) MCF-7 cells were transfected with a Ras-dominant positive vector (V12) and a Ras-dominant negative vector (N17). After 24 h, the cells were treated with E2 (10 nm) for 24 h, and then the cells were harvested. The expression of B4GALT1 was measured by performing RT-PCR and Western Blot analysis. (D) MCF-7 cells were treated with MAPK inhibitors, including SP600125 (20 μM), SB203580 (10 μM), and U0126 (5 μM). After 30 min, the cells were treated with E2 (10 nm) for 24 h. The cells were harvested and the expression of B4GALT1 was evaluated by performing RT-PCR and Western Blot analysis.

(Fig. 3A). In addition, ICI 182,780, a selective antagonist for both the intracellular and membrane-associated ERs [26], and theophylline 8-[(benzylthio)methyl]-(7CI,8CI) (TPBM), a potent inhibitor of ER-α binding to ERE site [27], inhibited the expression of B4GALT1 induced by estrogen treatment. In contrast, G15, a selective antagonist of the non-nuclear estrogen receptor GPR30 [25], had no effect on B4GALT1 expression (Fig. 3B). A Ras-dominant negative vector and specific inhibitors of MAPKs had no effect on estrogen-induced B4GALT1 expression (Fig. 3C and D). From these results, we suggest that estrogen-induced B4GALT1 expression is regulated through the classical estrogen signaling pathway and the direct binding of ER-α and the ERE site located on the B4GALT1 promoter.

3.3. Estrogen-induced B4GALT1 expression promotes the proliferation of MCF-7 cells

Estrogen is known as a potent regulator for promoting the proliferation of breast cancer cells [16]. Moreover, it has been reported that B4GALT1 expression can regulate cell proliferation functioning as both an enzyme producing Galβ1-4GlcNAc structures on membrane proteins, such as a focal adhesion kinase [7,28,29] and as a membranous receptor for the recognition of specific ligands [6,20]. However, there is still no direct evidence of the relationship between increased proliferation and estrogen-induced B4GALT1 expression. Thus, we knock-downed the *B4GALT1* gene to examine the possibility that B4GALT1 is responsible for promoting the proliferation of estrogen-treated MCF-7 cells. Among 3 different clones of siGalT vectors, only one clone successfully prevented the expression of B4GALT1 (Fig. 4A). The increased proliferation of estrogen-treated MCF-7 cells was significantly abolished by treatment with siGalT (Fig. 4B). In addition, cell cycle analysis showed that estrogen increased the percentage of G2/M phase cells in native MCF-7 cells, whereas the percentage was not increased by estrogen treatment in siGalT-treated MCF cells (Fig. 4C). These results suggest that the expression of B4GALT1 is a key regulator in estrogen-induced proliferation of MCF-7 cells.

We subsequently used specific antibodies against the B4GALT1 protein to inhibit the receptor function of B4GALT1 [30]. The results showed that only the C-terminal-specific antibody inhibited estrogen-stimulated proliferation of MCF-7 cells. In contrast, N-terminal-specific antibodies and secondary isotopic IgG did not show significant inhibition on the proliferation of the cells (Fig. 4D). These results are due to the exposure of the C-terminus to the outer cell surface, because B4GALT1 is a type II membrane protein [3]. It may be possible that enzymatic function also influences the proliferation of the cells. As there is no specific commercial inhibitor for the enzymatic activity of the B4GALT1 protein [31], we cannot directly determine the effect of B4GALT1 activity on cell proliferation. If the enzymatic activity had an influence on

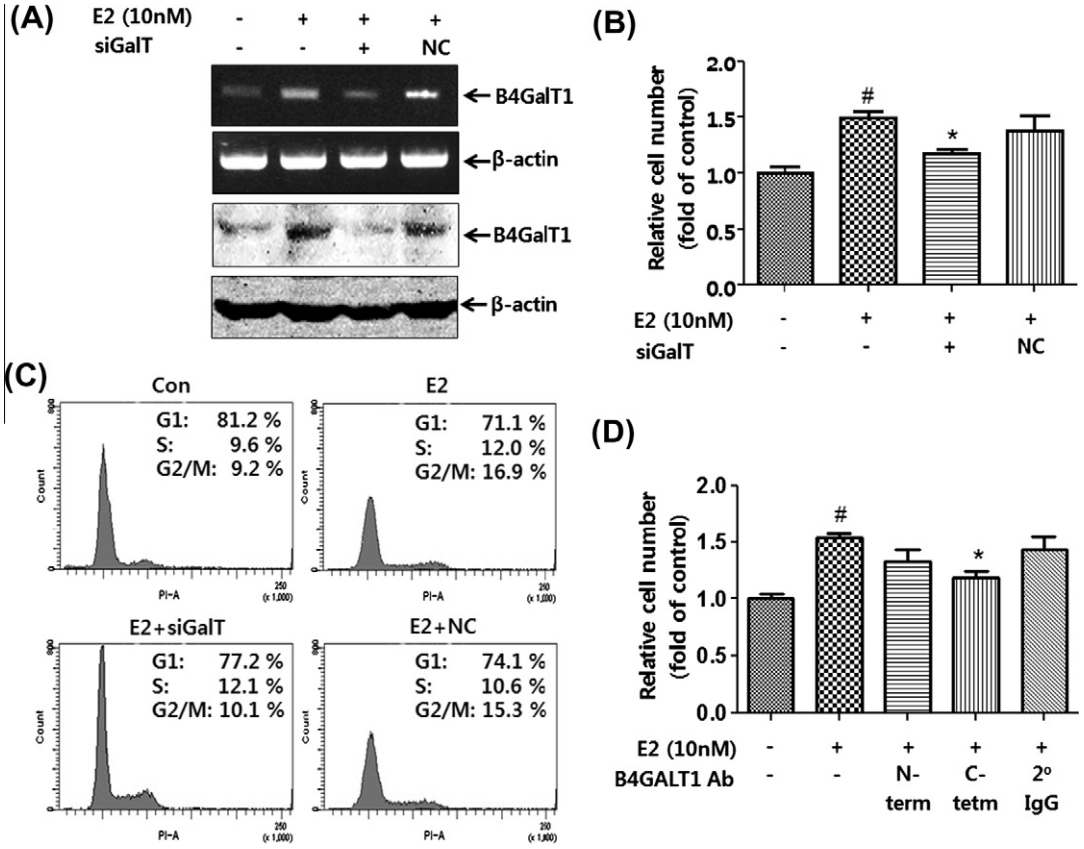

Fig. 4. The effect of B4GALT1 inhibition by siRNA or specific antibody on the regulation of MCF-7 cell proliferation. (A) The cells were transfected with siGalT for 24 h and subsequently stimulated with estrogen. After 24 h, the cells were harvested and the expression of B4GALT1 was estimated by RT-PCR and Western Blot analysis. (B) MCF-7 cells were grown in DCC-FBS for 24 h and subsequently treated with siGalT or scramble-siRNA (NC). After 24 h, the cells were treated with E2 (10 nm) for 72 h. Proliferation of the MCF-7 cells was measured by using the Countess Automated Cell Counter. $^{\#}P < 0.05$ on comparison with control group, and $^{*}P < 0.05$ on comparison with E2 group. (C) The effect of siGalT on the cell cycle regulation of MCF-7 cells was estimated by DNA content analysis by FACS analysis. (D) MCF-7 cells were grown in DCC-FBS for 48 h and subsequently treated with E2 (10 mM). In order to block cell surface B4GALT function, cells were treated with specific antibodies for B4GALT1 (N-terminal and C-terminal) and nonspecific secondary antibodies. After 72 h culturing, the proliferation of MCF-7 cells was measured by using the Countess Automated Cell Counter. $^{\#}P < 0.05$ on comparison with control group, and $^{*}P < 0.05$ on comparison with E2 group.

cell proliferation, it would also be abolished by siGalT transfection. Our results showed that C-terminal antibody treatment inhibited the proliferation of MCF-7 cells to the same extent as siGalT transfection. Thus, we supposed that estrogen-induced expression of B4GALT1 regulates the proliferation of MCF-7 cells, mainly by acting as a membrane receptor.

In conclusion, estrogen-induced B4GALT1 expression is regulated through the classical nuclear pathway and the binding of ER-α to the ERE site on promoter regions of the *B4GALT1* gene. In addition, estrogen-stimulated B4GALT1 expression plays a key role in the proliferation of MCF-7 cells through its activity as a membrane receptor. These results suggest that B4GALT1 might be a good molecular target for understanding estrogen-induced proliferation and for the response to therapeutics in ER-α-positive breast cancer cells.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.08.140.

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