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The histone demethylase LSD1 is required for estrogen-dependent S100A7 gene expression in human breast cancer cells

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ABSTRACT

S100A7, a member of S100 calcium binding protein family, is highly associated with breast cancer. However, the molecular mechanism of S100A7 regulation remains unclear. Here we show that long-term treatment with estradiol stimulated S100A7 expression in MCF7 breast cancer cells at both the transcriptional and translational levels. Both treatment with a histone demethylase LSD1 inhibitor and shRNA-based knockdown of LSD1 expression significantly decreased 17β-estradiol (E2)-induced S100A7 expression. These reduced E2-mediated S100A7 expression are rescued by the overexpressed wild-type LSD1 but not by its catalytically inactive mutant. Our data showed *in vivo* association of LSD1 with S100A7 promoters, confirming the potential role of LSD1 in regulating S100A7 expression. S100A7 knockdown increased both normal cell growth and estrogen-induced cell proliferation, suggesting a negative influence by S100A7 on the growth of cancer cells. Together, our data suggest that estrogen-induced S100A7 expression mediated by the histone demethylase LSD1 may downregulate breast cancer cell proliferation, implying a potential tumor suppressor-like function for S100A7.

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1. Introduction

S100A7 (psoriasin) belongs to the S100 family of calcium-binding EF-hand proteins and was originally identified as an mRNA overexpressed in psoriatic skin [1]. Although many lines of evidence suggest the relevance of S100A7 in carcinogenesis, its exact role is still controversial. Several reports support the idea that S100A7 functions as an oncogene. For example, induction of epidermal growth factor-dependent signaling pathway via S100A7 promotes metastasis and tumor growth [2]. In addition, the functional interaction of αvβ6 integrin with S100A7 is required to promote αvβ6-dependent invasive activity in oral squamous cell carcinoma, and the S100A7-dependent production of reactive oxygen species and expression of vascular endothelial growth factor are involved in endothelial cell proliferation [3,4]. S100A7 is overexpressed in squamous cell carcinoma of the skin, bladder, and head and in breast cancer [5–7]. In particular, high expression of S100A7 is observed in preinvasive ductal carcinoma *in situ* and is associated with poor outcome in estrogen receptor (ER)-negative invasive breast cancer [8–10]. The physical interaction of S100A7 and c-Jun activation domain-binding protein-1 may be involved in the increased expression of activator protein 1- and hypoxia-inducible factor 1-dependent genes, leading to breast cancer progression [10]. Although all these studies point to a tumorigenic function for S100A7 in ER-negative breast cancer cells, a recent report proposed the contrasting idea that S100A7 suppresses tumors through the β-catenin/T cell factor 4 protein pathway in ER-positive breast cancer cells [11]. To date, many reports have demonstrated the potential role of S100A7 in carcinogenesis. However, the mechanism by which S100A7 gene expression is regulated in breast cancer progression is not yet fully understood. Some evidence suggests that S100A7 expression is controlled by ER-β or by pro-inflammatory cytokines such as oncostatin-M and interleukin-6 Refs. [12,13]. Estrogen and its receptors are known to be involved in their target gene expression in breast cancer cells [14]. Study of how estrogen controls S100A7 expression may provide insights into understanding the role of S100A7 in breast cancer progression. In the present study, we show that S100A7 expression is induced in MCF7 cells by long-term estrogen exposure via the function of the histone demethylase LSD1. In addition, shRNA-based knockdown of S100A7 expression increased cell proliferation irrespective of estrogen treatment. Thus, our present data support the idea that S100A7 has tumor suppressor-like activity and that this activity is mediated by LSD1 in ER-positive breast cancer cells.

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2. Materials and methods

2.1. Cell culture

The human breast cancer cell line MCF7 was cultured in Minimum Essential Medium (Welgene, Korea) with 5% fetal bovine serum. Cells were treated with 3 mM pargyline (Sigma, USA) for 18 h and 10 nM 17β-estradiol (E2) (Sigma) for 72 h, as indicated.

2.2. shRNA and protein expression constructs

For the expression of shRNAs against LSD1, S100A7, and luciferase, the following oligonucleotides were annealed and cloned into a pLKO shRNA expression vector: for LSD1_A-shRNA 5′-CCG GGC TAC ATC TTA CCT TAG TCA TCT CGA GAT GAC TAA GGT AAG ATG TAG CTT TTT G-3′ and 5′-AAT TCA AAA AGC TAC ATC TTA CCT TAG TCA TCT CGA GAT GAC TAA GGT AAG ATG TAG C-3′); for LSD1_C-shRNA 5′-CCG GGC CTA GAC ATT AAA CTG AAT ACT CGA GTA TTC AGT TTA ATG TCT AGG CTT TTT G-3′ and 5′-AAT TCA AAA AGC CTA GAC ATT AAA CTG AAT ACT CGA GTA TTC AGT TTA ATG TCT AGG C-3′; for S100A7-shRNA 5′-CCG GGC TGA CGA TGA TGA AGG AGA ACT CGA GTT CTC CTT CAT CAT CGT CAG CTT TTT G-3′ and 5′-AAT TCA AAA AGC TGA CGA TGA TGA AGG AGA ACT CGA GTT CTC CTT CAT CAT CGT CAG C-3′; and for luciferase-shRNA 5′-CCG GAG AGC TGT TTC TGA GGA GCC TCT CGA GAG GCT CCT CAG AAA CAG CTC TTT TTT G-3′ and 5′-AAT TCA AAA AAG AGC TGT TTC TGA GGA GCC TCT CGA GAG GCT CCT CAG AAA CAG CTC T-3′. The sequence of each construct was verified before use.

2.3. RNA extraction, reverse transcriptase PCR (RT-PCR), and quantitative real time-PCR (qRT-PCR)

Total cellular RNA was extracted using the RNeasy Mini Kit (Qiagen, USA). cDNA was synthesized using RevertAid™ M-MuLV Reverse Transcriptase (Fermentas, USA) according to the manufacturer's protocol. qRT-PCR was performed with SYBR Premix Ex Taq II (Takara, Japan) and an ABI7000 sequence detector (Applied Biosystems, USA). The PCR primers used for S100A7 were 5′-GTC CAA ACA CAC ACA TCT CAC TCA-3′ and 5′-TCA TGC CTA TTA TGG ACC TCT CAG-3′ and those used for LSD1 were 5′-TTC CAC GAC TCT TCT TTG CGG G-3′ and 5′-AGC CCA CTC AGC AGA GCA CCA T-3′. The primers for GAPDH have been previously described [15].

2.4. Site directed mutagenesis

The plasmid expressing LSD1_WT (resistant) was constructed by introducing mutation into the coding sequence of LSD1_WT using the following primers: LSD1_WT (resistant) 5′-ATT GAA GTC TAG TTG GTG TGA TAA ATA GCT CGT TGC TTC TAG CAA CCG GTT -3′ and 5′-AAC CGG TTG CTA GAA GCA ACG AGCATAT TTA TCA CAC CAA CTA GAC TTC AAT -3′. For construction of LSD1_K661A (resistant), LSD1_WT (resistant) construct was used as template for introducing the mutation K661A using the following primers: LSD1_K661A (resistant) 5′-TTT GGC AAC CTT AAC GCG GTG GTG TTG TGT TTT -3′ and 5′-AAA ACA CAA CAC CAC CGC GTT AAG GTT GCC AAA -3′. PCR was performed with an accuprime Pfx DNA polymerase (Invitrogen). The PCR cycling parameters are 1 cycle of 2 min at 95 °C and 24 cycles of 15 s at 95 °C, 30 s at 52 °C, 1 min/kb of plasmid length at 68 °C. After PCR, the DpnI restriction enzyme was added directly to amplification reaction. Each reaction tube was incubated at 37 °C for 2 h to digest the parental supercoiled double-stranded DNA. The DpnI-treated DNA from each reaction was transferred to transformation reaction.

2.5. Western blot analysis

The cultured cells were washed and lysed with lysis buffer (10 mM Tris, pH 7.5, 150 mM NaCl, 0.2% Triton X-100, 0.2 mM Na_3VO_4, 0.3% NP-40, 1 mM PMSF) containing protease inhibitors (Roche, USA). Fifty micrograms of cell lysate protein was separated by 12% SDS–PAGE, transferred to a PVDF membrane, and immunoblotted with the following antibodies: L4793 (Sigma) against LSD1 (AOF2), ab27957 (Abcam, UK) against S100A4, sc52948 (Santa Cruz Biotechnology, USA) against S100A7, sc48352 (Santa Cruz Biotechnology) against S100A8, sc20173 (Santa Cruz Biotechnology) against S100A9, and LF-PA0018 (AB frontier, Korea) against GAPDH.

2.6. Chromatin immunoprecipitation (ChIP)

MCF7 cells were treated with E2 (10 nM for 72 h) or pargyline (3 mM for 18 h) before harvesting for ChIP that was performed using a Chromatin IP kit (Cell Signaling Technology, USA). DNA–protein complexes were precipitated using antibodies against LSD1 (Sigma). Immunoprecipitated DNA was amplified using SYBR Premix Ex Taq II (Takara). The PCR primers used to amplify the S100A7 promoter were 5′-GTC CAA ACA CAC ACA TCT CAC-3′ and 5′-GAC ATT TCC ACA GGA GTT GCC-3′; those for the S100A7 3′UTR were 5′-CCC AGC CCC ACC AAT GGG CCT-3′ and 5′-TC G GTG GGA GAA GAC ATT TT-3′.

2.7. Colony formation assay

Cells were seeded at 5×10^2 cells per well in 6-well plates in triplicate and then maintained for 14 days. Cells were fixed with fixation solution (7:1 methanol:acetic acid) for 10 min and stained with 0.02% crystal violet for 20 min; the cells were then photographed and counted.

3. Results

3.1. S100A7 is expressed at high levels after long-term treatment of MCF7 cells with E2

To determine the effects of estrogen on S100A7 gene expression, we measured S100A7 mRNA levels after MCF7 cells were treated with E2 for various lengths of time. Short exposure to E2 (60 min) was insufficient to induce S100A7 gene expression (Fig. 1A), while longer exposures to E2 (36–72 h) resulted in markedly increased S100A7 mRNA levels, which peaked three days after treatment with E2 (Fig. 1B and C). In contrast, mRNA expression of other calcium-binding protein family genes such as S100A4, S100A8, and S100A9 genes was not induced by E2, irrespective of the duration of exposure (Fig. 1). Furthermore, the up-regulation of S100A7 protein expression, but not that of S100A4, S100A8 and S100A9, was also confirmed (Fig. 1D). Together, these results suggest that S100A7 is an estrogen-regulated gene in MCF7 breast cancer cells.

3.2. Inhibition or depletion of the histone demethylase LSD1 blocks E2-induced S100A7 gene activation

Because a previous report showed that the histone demethylase LSD1 is required to induce E2-dependent gene expression [16], we investigated whether LSD1 is associated with E2-dependent S100A7 expression. First, we treated MCF7 cells with pargyline, a well-known LSD1 inhibitor that blocks LSD1-mediated demethylation [17]. Inhibition of LSD1 demethylase activity by pargyline significantly reduced the E2-mediated S100A7 expression but did not

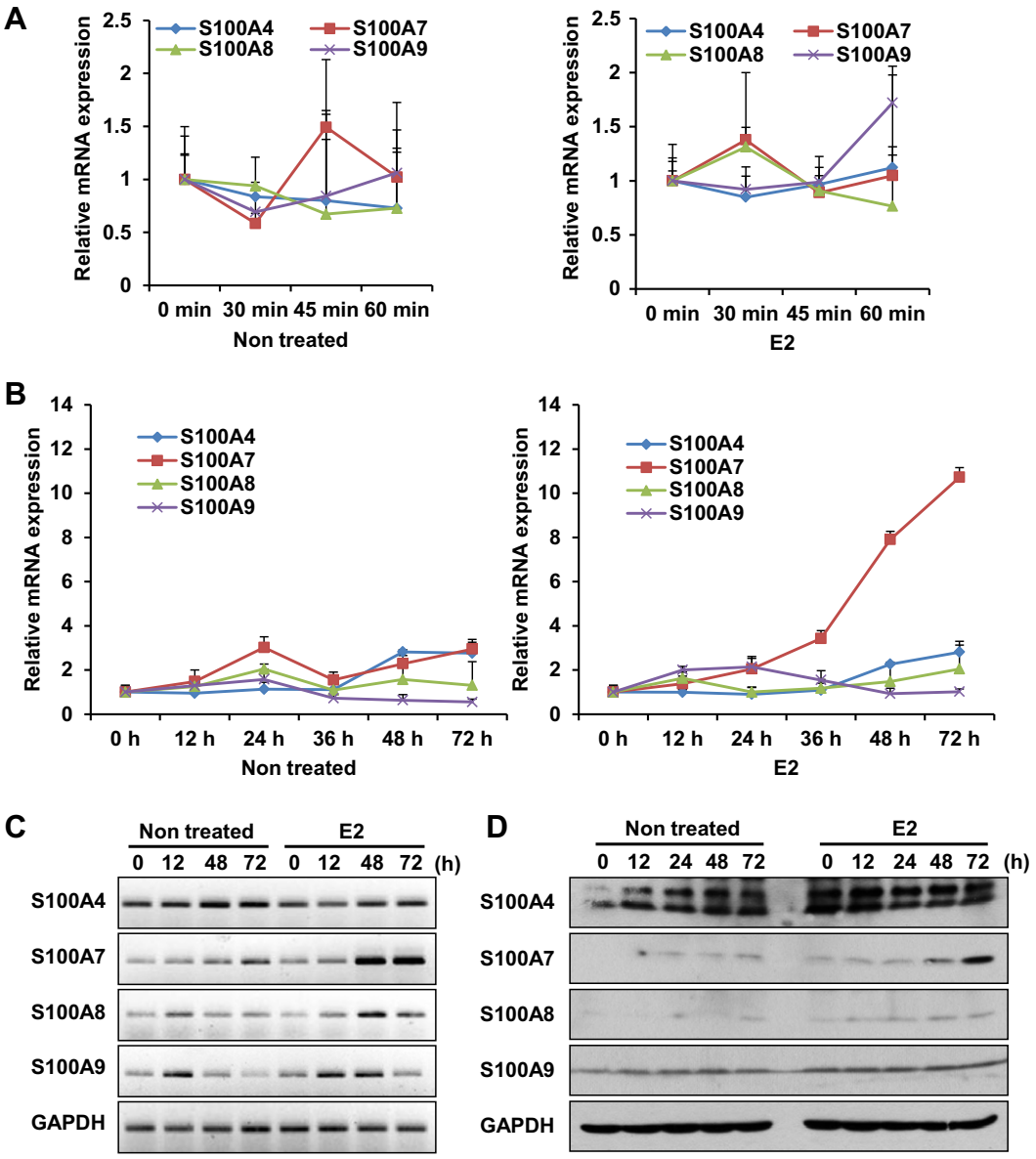

Fig. 1. The induction of S100A7 expression in MCF7 cells by long-term treatment with 17β-estradiol (E2). (A and B) qRT-PCR analysis of S100A4, S100A7, S100A8 and S100A9 expression in MCF7 cells with or without E2 treatment for the short or long durations indicated. The values represent the mean ± S.D. of three independent experiments, each with three technical replicates. (C and D) Semi-quantitative RT-PCR and Western blot analyses of mRNA and protein expression of S100A4, S100A7, S100A8 and S100A9 in MCF7 cells with and without E2 treatment for the short or long durations indicated.

significantly affect the expression of S100A4, S100A8, or S100A9 (Fig. 2A and B). Consistent with these observations, the depletion of LSD1 by shRNA knockdown also markedly decreased E2-mediated S100A7 induction (Fig. 2C and D). Thus, our data suggest that LSD1 is involved in the regulation of S100A7 gene expression by estrogen.

3.3. LSD1 binds to the promoter of the S100A7 gene

Because a previous report showed that LSD1 physically associates with promoter regions of genes whose expression is E2-dependent to affect the regulation of these genes [16], we employed a ChIP assay to determine whether LSD1 can associate with the promoter region of the S100A7 gene. When we assayed E2-treated or untreated cells using the ChIP assay with an anti-LSD1 antibody, we observed that LSD1 occupies a significant portion of the S100A7 gene promoter region. In contrast, LSD1 is not present at the gene's 3′-UTR region, irrespective of E2 treatment (Fig. 2E). Thus, our data demonstrate that LSD1 can associate with the S100A7 promoter region, consistent with LSD1's involvement in E2-dependent induction of S100A7 transcription.

3.4. LSD1 demethylase activity is required for E2-induced S100A7 gene expression

To further investigate the direct involvement of LSD1 demethylase activity in E2-dependent S100A7 gene expression, we took advantage of two LSD1 constructs: shRNA-resistant wild-type (WT) LSD1 and shRNA-resistant catalytically inactive mutant LSD1 (K661A) [18]. The shRNA-resistant WT LSD1 overexpressed cells were able to reverse the decreased expression of S100A7 by LSD1 knockdown whereas cells overexpressing shRNA-resistant inactive mutant LSD1 (K166A) did not rescue the decreased status of E2-induced S100A7 gene expression (Fig. 3). These data support

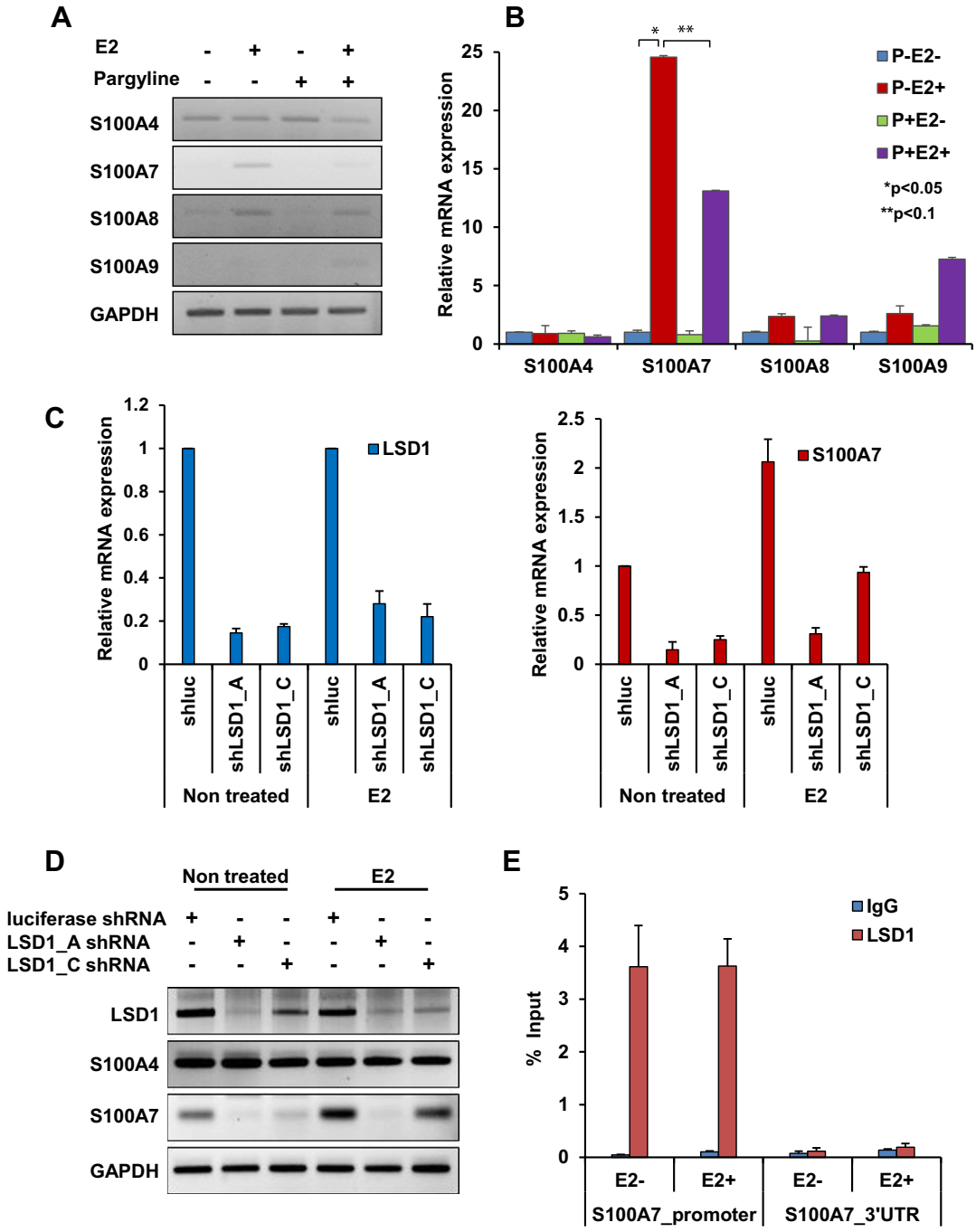

Fig. 2. The histone demethylase LSD1 is required for S100A7 expression in MCF7 cells. (A) Semi-quantitative RT-PCR analysis of S100A4, S100A7, S100A8 and S100A9 gene expression in MCF7 cells treated with E2 and/or an inhibitor of LSD1 (pargyline). (B) The mRNA levels of cells treated as in (A) were assessed by qRT-PCR. The values represent the mean ± S.D. of two independent experiments, each with three technical replicates. (C) MCF7 cells were transiently infected with control luciferase shRNA (shluc) or LSD1 shRNA (shLSD1_A or shLSD1_C) viral particles. After 48 h, cells were treated with or without E2, and qRT-PCR was performed. (D) The mRNA levels of LSD1, S100A7, and other control genes were assessed by RT-PCR in cells treated as in (C). (E) ChIP assay to examine whether LSD1 protein occupies the S100A7 promoter region. MCF7 cells were treated with or without E2, and ChIP analysis was performed using anti-LSD1 antibodies. The values represent the mean ± S.D. of two independent experiments, each with three technical replicates. Symbols used: P, pargyline; E, estradiol; −, non-treated; +, treated.

that the demethylase activity of LSD1 protein is essential for estrogen-mediated S100A7 gene expression.

3.5. S100A7 suppresses cell proliferation during both normal growth and/or estrogen-dependent cell growth

E2 promotes breast cancer cell proliferation *in vivo* and *in vitro* [19]. Furthermore, a recent report suggested that S100A7 overexpression inhibits cell proliferation through the β-catenin/T cell factor 4 protein pathway in ER-positive MCF7 breast cancer cells [11]. Thus, we assessed whether S100A7 is involved in E2-dependent MCF7 cell proliferation by establishing an MCF7 cell line stably expressing a lentiviral shRNA plasmid that knocks down S100A7 expression. The knockdown of S100A7 expression was confirmed by RT-PCR (Fig. 4A). Consistent with previous studies, MCF7 cells stably expressing a control shRNA against a luciferase gene

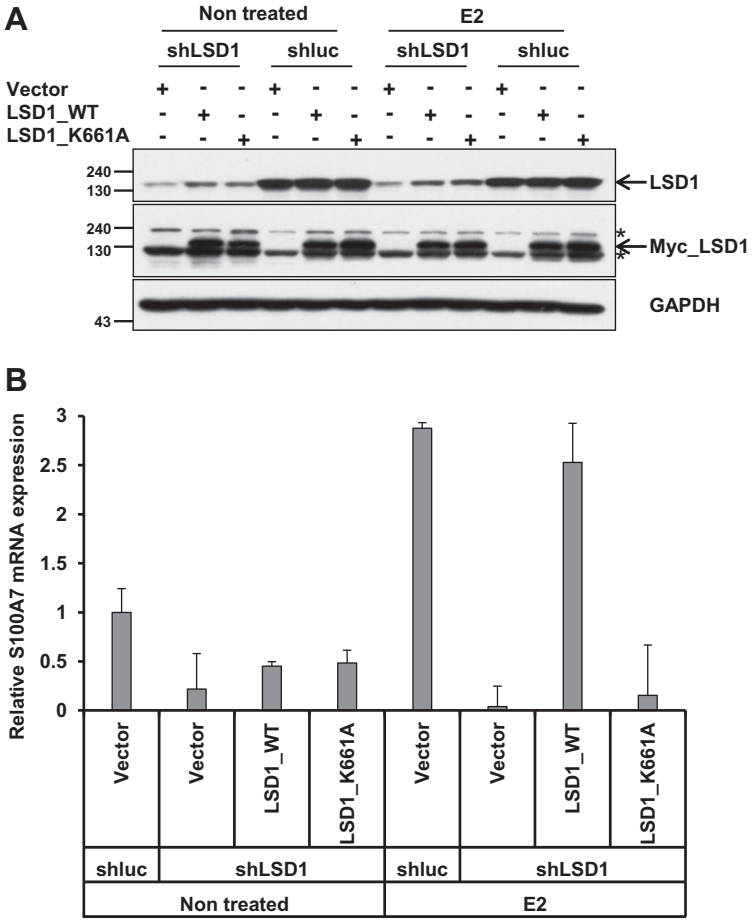

Fig. 3. The demethylase activity of LSD1 is important for E2-mediated S100A7 expression in MCF7 cells. (A) MCF7 cells stably expressing either control luciferase shRNA or LSD1 shRNA were transfected with vector, or LSD1_WT (resistant), or LSD1_K661A (resistant) construct. The transfected cells were treated with or without E2, two-day after transfection. Whole-cell extracts of the transfected MCF7 cells were analyzed by Western blot analysis using antibodies against LSD1, Myc, and GAPDH. The asterisks represent nonspecific bands. (B) For cells treated as in (A), the mRNA levels of S100A7 and other control genes were assessed by qRT-PCR. Error bars represent the standard deviation from three technical replicates. The data are representative of two independent experiments.

exhibited markedly increased colony formation after E2 treatment (Fig. 4B) compared with cells stably expressing a S100A7-shRNA in which S100A7 expression was decreased. S100A7 knockdown in MCF7 cells promoted the formation of colonies of all sizes, suggesting a role for S100A7 as a tumor suppressor under normal growth conditions (Fig. 4B and C). Interestingly, the fold increase in the number of small colonies (less than 1 mm in diameter) of the S100A7 knockdown cells treated with E2 was less than that of control knockdown cells, while the fold increase in the number of large colonies (more than 1 mm in diameter) of S100A7 knockdown cells treated with E2 was comparable to that of the control knockdown cells (Fig. 4C). Together, these results suggest that S100A7 may negatively regulate cell proliferation during both normal growth and/or estrogen-dependent cell growth.

4. Discussion

Previous studies demonstrate that estrogen may control the transcription of target genes by binding estrogen receptors; moreover, LSD1 can demethylate both histone H3-Lys 4 and H3-Lys 9 [17,20]. Interestingly, it has been reported that histone H3-Lys 9-me2 demethylation at most ERα target genes in MCF7 cells by LSD1 triggers DNA oxidation, leading to estrogen-induced gene expression [16]. Expression of S100A7 is associated with breast cancer and also occurs in inflammatory cells [7,21]. In particular, S100A7 is strongly associated with ERα-negative tumors and S100A7 transcription exhibits an estrogen-dependent profile in human breast cancer cells [8–10,13]. However, the mechanism by which S100A7 gene expression is regulated in breast cancer cells remains unclear.

In the present study, we have shown that the histone demethylase LSD1 is involved in estrogen-induced transcription of the S100A7 gene in MCF7 breast cancer cells. Deficiency of LSD1 activity caused either by shRNA knockdown or inhibition of its enzymatic activity by the small molecule inhibitor pargyline significantly decreased estrogen-induced S100A7 expression in MCF7 breast cancer cells. Moreover, LSD1 was shown by ChIP assay to associate with the promoter region of S100A7 irrespective of estrogen treatment, implying a potential role for LSD1 in the transcriptional regulation of S100A7 via chromatin modulation. In addition, our data showed that the reduced E2-induced S100A7 expression by LSD1 knockdown was rescued by introduction of shRNA-resistant LSD1 WT but not by shRNA-resistant inactive mutant LSD1 (K661A). These data support that the demethylase activity of LSD1 is essential for the E2-dependent induction of S100A7. Although histone H3-Lys 9 methylation at the S100A7 promoter was significantly decreased in response to estrogen treatment and histone H3-Lys 4 methylation levels increased, histone H3-Lys 9 methylation during estrogen treatment was not reversed by either treatment with the LSD1 inhibitor pargyline or LSD1-knockdown (Supplementary Fig. S1; data not shown). In addition, we found that estrogen-induced S100A7 expression was not

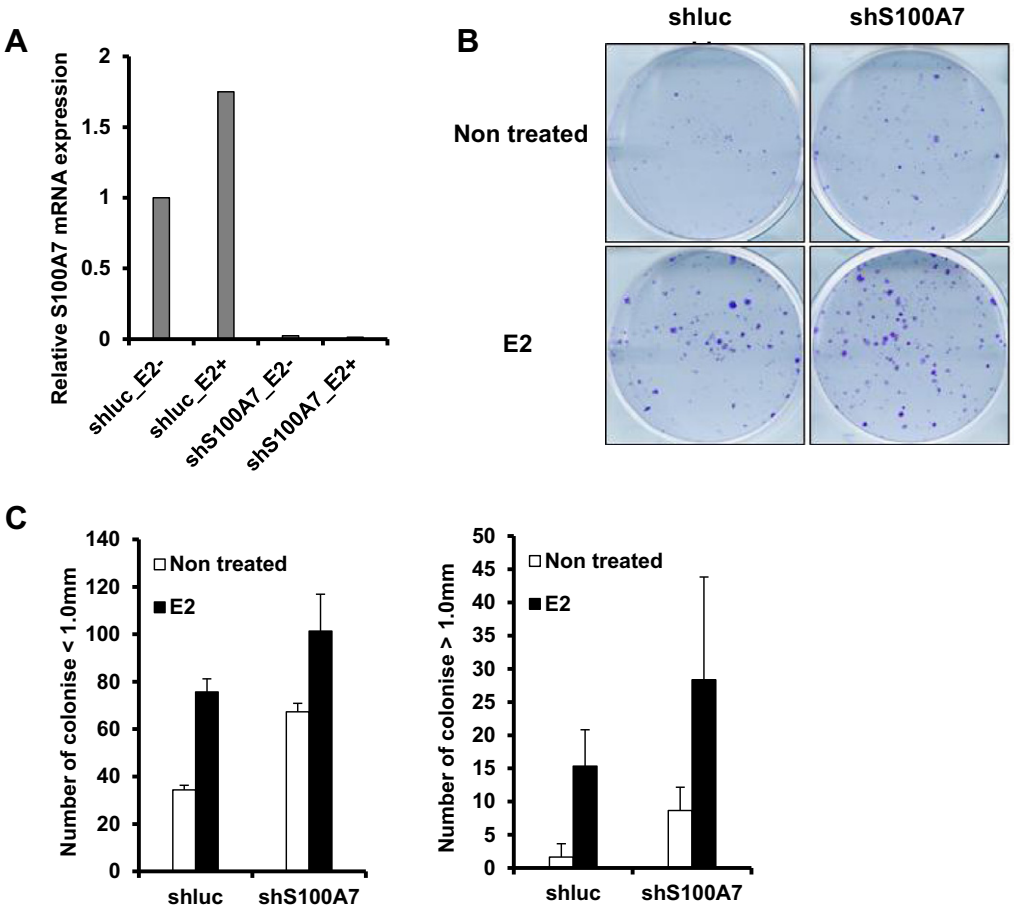

Fig. 4. S100A7 inhibits E2-induced MCF7 cell proliferation. (A) RT-PCR verification of S100A7 knockdown by shRNA. Stable control knockdown cells (shluc) and S100A7 knockdown cells (shS100A7) were established and used for total RNA extraction. Total RNAs from both cell lines were used for measuring the S100A7 mRNA level. (B) The effect of LSD1 knockdown on the ability of MCF7 cells to form colonies. In the colony formation assay, control knockdown cells (shluc) and S100A7 knockdown cells (shS100A7) were cultured for 14 days in the absence or presence of E2, stained with crystal violet, and photographed. (C) The number of colonies with a diameter more than 1 mm or less than 1 mm was calculated in three independent experiments. Symbols used: E2, estradiol; −, non-treated; +, treated.

affected by knockdown-dependent deficiency of another histone demethylase, Jumonji C domain-containing oxygenase D2C (JMJD2C), which is known to cooperatively regulate the function of LSD1 at androgen receptor-dependent target promoters (Supplementary Fig. S2 and Ref. [22]). These results suggest different modes of LSD1 function in androgen- and/or estrogen-induced transcription pathway(s). Thus, we hypothesized that LSD1 indirectly regulates S100A7 expression in MCF7 cells by switching the on/off state of as yet unidentified transcription factor(s) in a (de)methylation-dependent manner. Some evidence led us to select the signal transducer and activator of transcription-3 (STAT3) transcription factor as a candidate: the transcriptional level of STAT3 is increased in mouse liver after long-term E2 treatment [23] and the methylation-demethylation cycle of STAT3 controlled by SET domain protein 9 and LSD1 mediates the transcription of target genes [24]. Therefore, we assayed for an association of LSD1 with STAT3 during E2-dependent S100A7 transcriptional regulation in MCF7 cells. However, our data suggest that STAT3 does not cooperate with LSD1 to regulate S100A7 expression, although a potential involvement of STAT3 in the regulation of S100A7 expression cannot be completely excluded (Supplementary Fig. S3). A recent report suggested that S100A7 possesses tumor-suppressive activity, acting through the β-catenin/TCF4 pathway in ERα positive breast cancer cells [11]. Consistent with the previous study, we observed that S100A7 knockdown significantly increased ERα-positive breast cancer cell proliferation irrespective of estrogen treatment (Fig. 4). Thus, it is possible that β-catenin/TCF4 partners with LSD1 mediate estrogen-induced S100A7 expression. Because estrogen regulates many target genes in MCF7 cells [25], the increased breast cancer cell proliferation induced by S100A7 knockdown is likely not the only effect of estrogen-induced target gene expression. Although further studies are needed to clarify the mechanisms by which LSD1 regulates S100A7, our data suggest that the LSD1-S100A7 axis may be functionally linked to E2-induced breast cancer cell proliferation.

In conclusion, we have demonstrated that S100A7 is up-regulated in response to estrogen in MCF7 breast cancer cells. More importantly, we show for the first time that the histone demethylase LSD1 plays a key role in the transcriptional activation of S100A7 gene expression. Moreover, we suggest that S100A7 inhibits estrogen-mediated cell proliferation of MCF7 breast cancer cells.

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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.2012.09.057.

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