The role of deubiquitinase PSMD7 in adipogenesis

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ABSTRACT

The role of deubiquitinase PSMD7 in adipogenesis

The ubiquitin–proteasome system (UPS) plays a fundamental role in protein turnover and metabolic regulation; however, the specific, non-canonical functions of individual proteasome subunits in adipogenesis remain largely unexplored. Here, we identify PSMD7, a 19S regulatory subunit of the 26S proteasome and a deubiquitinase (DUB), as a previously unrecognized regulator of adipocyte differentiation. We demonstrate that PSMD7 may exert non-canonical functions by regulating the stability of adipogenic factors.

PSMD7 expression was significantly upregulated in metabolically active tissues—including liver, gonadal white adipose tissue (gWAT), and inguinal white adipose tissue (iWAT)—in mice subjected to a high-fat diet. In 3T3-L1 preadipocytes, PSMD7 expression increased progressively during differentiation, parallel with lipid accumulation. Functional knockdown of PSMD7 impaired adipogenesis, as shown by reduced lipid droplet formation and downregulation of adipogenic markers such as C/EBPα, C/EBPβ, PPARγ, FASN, and FABP4.

Mechanistically, PSMD7 interacted with and deubiquitinated SREBP1, a master transcription factor in lipogenic gene expression. PSMD7 depletion led to enhanced ubiquitination and proteasomal degradation of SREBP1, accompanied by decreased expression of its downstream targets, including FASN, ACC1, SCD1, and ACYL. These findings indicate that PSMD7 promotes adipocyte differentiation, potentially by maintaining SREBP1 protein stability.

Altogether, our study reveals a novel PSMD7–SREBP1 regulatory axis that controls adipogenesis, expanding the functional repertoire of proteasome subunits beyond their traditional roles in protein degradation. This work provides new insight into adipocyte biology and highlights PSMD7 as a potential therapeutic target for obesity and metabolic disease.

Key words: PSMD7, SREBP1, Proteasome, Ubiquitinase, PTMs, Adipogenesis

1. Introduction

Metabolic diseases have now become a major public health concern due to their prevalence rates which have significantly risen over the past two decades[1,2]. Obesity is one of the most prevalent diseases, defined as an excessive build-up of body fat with a body mass index (BMI) of ≥30 kg/m^2[3]. According to WHO, around 1 billion people worldwide are obese, and this is expected to increase continuously, reaching 1.77 billion people by 2035[4,5]. Additionally, obesity is frequently linked to other metabolic conditions such as non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2D), and even cancers, making it responsible for the death of 120 million adults each year[5]. Thus, the most effective approach to avoid the development of various comorbidities is through the prevention and early management of obesity[6].

At a cellular level, obesity is closely linked to the dysregulation of adipogenesis—the process by which preadipocytes transform into mature adipocytes[7]. The function of adipocytes is strongly associated with metabolic health, as it regulates lipid storage, energy balance, and insulin sensitivity[8,9].

Among the transcriptional regulators involved in adipogenesis, sterol regulatory element-binding protein 1 (SREBP1) is particularly important due to its role in promoting fatty acid production and lipid accumulation. SREBPs constitute a family of transcription factors that play a vital role in maintaining lipid homeostasis by generating SREBP1 and SREBP2, which are encoded by the *SREBF1* and *SREBF2* genes, respectively. While SREBP2 is responsible for cholesterol metabolism, SREBP1 is known to be involved in fatty acid production and adipogenesis regulation[10,11]. Two isoforms of SREBP1 have been discovered so far, including SREBP1a, predominantly found in the spleen, small intestine, and heart, along with the SREBP1c isoform expressed in the liver and adipose tissue[12,13]. Other essential transcription factors involved in adipogenesis include the CCAAT enhancer binding protein (Cebp) gene family, and peroxisome proliferator-activated receptor γ (PPARγ)[14,15].

Disruption in the regulation of adipogenesis contributes to ectopic lipid accumulation in tissues such as the heart, liver, and skeletal muscle, which is associated with an increased risk of insulin resistance and cardiovascular disorders[3,16]. In addition to that, obesity is also characterized by adipocyte hypertrophy, marked by an increase in the size of mature adipocytes, and hyperplasia,

reflected by a rise in the number of newly differentiated adipocytes[3]. Thus, understanding the molecular mechanisms that regulate adipogenesis is critical for developing therapeutic strategies to combat obesity and its associated diseases.

In addition to transcriptional regulation, adipogenesis and fat accumulation are tightly controlled by post-translational modifications (PTMs)[17]. PTMs alter protein conformation, localization, activity, stability, charge, and interactions with other biomolecules, thereby playing a critical role in determining cellular phenotypes and regulating various biological processes[18]. Among these, ubiquitination by the ubiquitin-proteasome system (UPS) is particularly critical for cellular homeostasis[19].

The UPS is responsible for degrading the majority of misfolded or defective cellular protein through the covalent attachment of Ub monomers (monoubiquitination) or Ub chains (polyubiquitination) to protein[18]. Ubiquitinated proteins are targeted for degradation by the 26S proteasome, a complex consisting of the 20S core and the 19S regulatory particle[20]. The 19S regulatory particle consists of the lid and base part and is responsible for recognizing, unfolding, and transferring the substrates into the 20s core particle, leading to the degradation of ubiquitinated proteins[21].

Importantly, ubiquitination is a reversible reaction, and the ubiquitinated protein is further regulated by deubiquitinates (DUBs), for the removal of ubiquitin tags and stabilize proteins[18]. Several DUBs have been recognized as a key regulator of lipid metabolism by regulating the turnover of proteins and lipids in the process of lipid metabolism[22,23]. USP1 is known to directly deubiquitinase C/EBPβ, leading to adipogenesis and lipid accumulation[24]. USP15 is also known to interact with proteins related to protein metabolisms, including the FABPs and perilipin by deubiquitinates the proteins, enhancing their stability, and increasing the lipid accumulation, which also leads to the development of NAFLD/NASH[25]. However, despite the growing interest in research on DUBs, the role of proteasome-associated DUBs in adipogenesis remains poorly understood.

PSMD7 (Proteasome 26S Subunit, Non-ATPase 7) is an ATP-independent component of the 19S regulatory particle, traditionally known for its role in recognizing and unfolding ubiquitinated proteins for degradation[26]. Additionally, PSMD7 is also a member of JAMM/MPN domain-associated metallopeptidase (JAMM) DUB family[27]. The role of PSMD7 is mainly explored in cancer, as the high expression level of it connected with worse progression in lung cancer, bladder cancer, pancreatic cancer, and breast cancer[26,28–30]. PSMD7 expression was significantly up-

regulated in head and neck squamous cell carcinoma, and found at the early development of cancer, making it a good marker for early diagnosis[31].

Additionally, PSMD7 is also known to promote gastric cancer cell proliferation, migration, and invasion, along with its resistance to chemotherapy drugs through deubiquitinating and stabilizing RAD23 homolog B (RAD23B)[32]. PSMD7 is also known to promote the stabilization of Ras-related protein Rab-1A (RAB1A), thus enhancing the proliferation and migration of bladder cancer[28]. Although PSMD7's primary function has been associated with proteasomal degradation, there is growing interest in understanding the potential non-canonical roles of proteasome subunits in regulating cellular processes beyond protein degradation.

Previous research has demonstrated that PSMD1 and PSMD2, members of the lid part of 19S, facilitate cellular lipid accumulation by regulating SREBP1, and the knockdown of PSMD1 and PSMD2 has been shown to reduce the formation of cellular lipid droplets by regulating SREBP1, independent of their role in proteasomal degradation[33]. These findings suggest that individual proteasome subunits may possess regulatory roles outside of the 26S proteasome, particularly in lipid metabolism. However, whether other lid subunits, such as PSMD7, play a similar role in adipogenesis remains unknown.

Given this gap, our study proposes the novel hypothesis that PSMD7 regulates adipogenesis during adipocyte differentiation, potentially by stabilizing key adipogenic regulators. We demonstrate that PSMD7 expression was upregulated during 3T3-L1 adipocyte differentiation and correlated positively with adipogenic marker expression. Furthermore, we identified SREBP1 as a novel PSMD7-interacting protein and demonstrated that PSMD7 stabilizes SREBP1 through deubiquitination. Immunofluorescence analysis revealed that PSMD7 and SREBP1 co-localized during 3T3-L1 adipocyte differentiation. These findings establish PSMD7 as a critical modulator of adipogenesis through SREBP1 stabilization, revealing a previously unrecognized regulatory function of the ubiquitin-proteasome system in adipocyte biology.

2. MATERIALS AND METHODS

2.1. Cell culture and adipocyte differentiation

AML12 and 3T3-L1 cells were generously provided by Professor Jae Woo Kim (Yonsei University, South Korea). For adipogenic differentiation, 3T3-L1 preadipocyte cells were first maintained in Dulbecco's Modified Eagle's Medium (DMEM; Welgene, Korea), with the addition of 10% Bovine Serum (BS) and 1% penicillin-streptomycin (PS) (Invitrogen, Carlsbad, CA, USA). After 48 hours (designated as day 0), to induce differentiation, 3T3-L1 cells were treated with a standard differentiation mixture (MDI), which included DMEM supplemented with 10% Fetal Bovine Serum (FBS, Corning Cellgro) and 1% PS, 1 μM dexamethasone, 1 μg/mL insulin, and 520 μM IBMX for 48 hours. This was followed by an additional 48 hours culturing the cells in DMEM supplemented with 10% FBS, 1% PS and the addition of 1 μg/mL insulin. The medium was then replaced with DMEM supplemented with 10% FBS and 1% PS, and changed every 2 days for up to 6 days of differentiation. For AML12 cells, cells were maintained in a DMEM: Ham's F12 medium (1:1) with 10% FBS, 1% PS, 5 ng/mL selenium, 40 ng/mL dexamethasone, 0.005 mg/mL transferrin, and 0.005 mg/mL insulin. All cell cultures were incubated with 5% CO2 at 37°C.

2.2. Transfection of small interfering RNA

For gene silencing, PSMD7-targeting siRNA (20 nM) was introduced into undifferentiated 3T3-L1 and AML12 cells using Lipofectamine RNAiMAX (Invitrogen, Carlsbad, CA, USA), according to the recommended procedure. For 3T3-L1 cells, the medium was changed with DMEM containing 10% BS 24 hours after transfection. Meanwhile, the AML12 cell media was changed 6 hours post-transfection with F12 media supplemented with necessary supplements.

2.3. Oil Red O Staining

The lipid droplet accumulation in differentiated 3T3-L1 cells was assessed by Oil Red O staining. The differentiated cells were washed with DPBS and then fixed for in 10% formalin for 10 minutes. Following fixation, the cells were washed with distilled water, and then 60% isopropanol, and allowed to dry completely. For staining, the Oil Red O (ORO) solution was prepared by diluting a

stock solution (0.35 g/100 mL) in isopropanol to a final concentration of 60% ORO working solution. The dried cells were then incubated at room temperature for 30 minutes with Oil Red O working solution, followed by three washes with distilled water. Lipid accumulation was quantified using ImageJ software.

2.4. Western Blot Analysis

Cells were extracted using RIPA lysis buffer composed of 1% Triton X-100, 50 mM Tris-HCl (pH 7.5), 2 mM EDTA (pH 8.0), 1% sodium deoxycholate, 0.1% sodium dodecyl sulfate, and 150 mM NaCl. The lysates were incubated for 20 minutes on ice and then centrifuged at 13,200 rpm for 25 minutes at 4°C. Protein levels were quantified using Pierce™ BCA Protein Assay Kit (Thermo Scientific, Waltham, MA, USA) following the manufacturer's instructions. The loading buffer was added, followed by boiling the lysate at 95 °C for 10 minutes. Proteins were separated by SDS-PAGE, and transferred onto nitrocellulose membranes (Merck Millipore, Billerica, MA, USA). The membranes were blocked in 5% BSA for 1 hour at room temperature and then incubated overnight at 4 °C with primary antibodies against PSMD7, PPARγ, C/EBPα, C/EBPβ, SREBP1, FASN, β-actin (Santa Cruz Biotechnology, Dallas, TX, USA), and FABP4 (Cell Signaling Technology, Danvers, Massachusetts, USA). The following day, membranes were washed five times with PBST (PBS + 0.05% Tween-20) for 10 minutes each, followed by incubation with horseradish peroxidase-conjugated secondary antibodies (Bethyl Laboratories, Montgomery, TX, USA) raised against the host species of the primary antibody for 1 hour at room temperature. Protein bands were visualized using the FUSION SOLO imaging system (Vilber, Eberhardzell, Germany), and β-actin was used as the internal loading control.

2.5. Co-immunoprecipitation and Ubiquitin assay

Cell lysates were prepared using an immunoprecipitation buffer containing 250 mM Tris-HCl (pH 7.5), 750 mM NaCl, 1% Triton X-100, 1.5% NP-40, 5 mM EGTA, and 5 mM EDTA, and the lysates were incubated for 20 minutes on ice and then centrifuged at 13,200 rpm for 25 minutes at 4°C. The protein quantification was done using Pierce™ BCA Protein Assay Kit (Thermo Scientific, Waltham, MA, USA). Protein lysate (1000-2000 ug) was incubated at 4 °C overnight on a rotor with the antibody of anti-PSMD7 and anti-SREBP1, along with anti-normal IgG (negative control) independently. The next day, protein A/G agarose beads (Santa Cruz Biotechnology) were added to

the supernatants and incubated at 4 °C for 2 hours on a rotor. Thereafter, the samples were washed 3 times with an immunoprecipitation buffer. Then, 2× protein loading dye was added, and the samples were heated at 95 °C for 5 minutes. After boiling, the samples were centrifuged, and the supernatants were used for Western blotting. Ubiquitin assays were performed as described previously[34].

2.6. RNA isolation and quantitative reverse transcription-PCR (qRT-PCR)

Total RNA was isolated using the RNA lysis reagent (Intron Biotechnology, Korea) according to the manufacturer's protocol. Complementary DNA (cDNA) synthesis was carried out using the RT-PCR master mix (TOYOBO, Osaka, Japan). The following primers was used: PSMD7, forward: 5'-TCTCCCAGCGGATCACAAAC-3' and reverse: 5'-TGATCTGGTGGTTGATGGGC-3', C/EBPα, forward: 5'-GACATCAGCGCCTACATCGA-3' and reverse: 5'-TCGGCTGTGCTGGAAGAG-3', C/EBPβ, forward: 5'-CCAGCTGAGCGACGAGTACA-3' and reverse: 5'-GCTTGAACAAGTTCCGCAGG-3', PPARγ, forward: 5'-AGGGCGATCTTGACAGGAAA-3' and reverse: 5'-CGAAACTGGCACCCTTGAAA-3', SREBP1, forward: 5'-GGAGCCATGGATTGCACATT-3', and reverse: 5'-GGCCCGGGAAGTCACTGT-3', FASN, forward: 5'-TGGGTTCTAGCCAGCAGAGT-3' and reverse: 5'-ACCACCAGAGACCGTTATGC-3', FABP4, forward: 5'-CATCAGCGTAAATGGGGATT-3' and reverse: 5'-TCGACTTTCCATCCCACTTC-3', ACC1, forward: 5'-ATGCGATCTATCCGTCGGTG-3', and reverse: 5'-TCCTCCAGGCACTGGAACT-3', SCD1, forward: 5'-GTACCGCTGGCACATCAACT-3', and reverse: 5'-AAGCCCAAAGCTCAGCTACTC-3', ACYL, forward: 5'-GAAGCTGACCTTGCTGAACC-3', and reverse: 5'-CTGCCTCCAATGATGAGGAT-3', and β-actin forward: 5'-GGCTGTATTCCCCTCCATCG-3', and reverse: 5'-CCAGTTGGTAACAATGCCATGT-3'. Quantitative RT-PCR was conducted using SYBR Premix Ex Taq (Clontech Laboratories, Mountain View, CA, USA) on ABI instruments (Applied Biosystems, Inc., Foster City, CA, USA). β-actin expression was used as the reference for normalizing gene expression levels.

2.7. Immunofluorescence

3T3-L1 cells were seeded onto 8-well chamber slides and allowed to adhere for 24 hours. Cells were then fixed with 4% paraformaldehyde (PFA) in PBS for 10 minutes at room temperature with gentle agitation, followed by three washes with ice cold PBS containing 0.1% Tween-20. To quench residual PFA, cells were incubated with 0.1 M glycine (pH 3.5) for 10 minutes, followed by permeabilization with 0.5% Triton X-100 in PBS for 10 minutes, washed three times and blocked in 1% BSA diluted in PBS containing 0.1% Tween-20 for 1 hour at room temperature. Cells were then incubated overnight at 4°C with primary antibodies against PSMD7 (Santa Cruz Biotechnology, Dallas, TX, USA), SREBP1 (Invitrogen), or normal IgG (negative control), diluted in blocking buffer. After washing, cells were incubated with Alexa Fluor 488- and Alexa Fluor 549-conjugated secondary antibodies (Invitrogen) for 1 hour at room temperature in the dark. Nuclei were counterstained using VECTASHIELD mounting medium containing DAPI (Vector Laboratories, Burlingame, CA, USA).

2.8. Mouse experiments

Male C57BL/6 mice (6 weeks old) were purchased from OrientBio (Seongnam, Korea) and acclimated for one week under standard conditions (12-hour light/dark cycle) and *libitum* access to food and water. After the acclimation period, the mice were randomly assigned to receive either a standard chow diet (CD) or a 60% high-fat diet (HFD; Research Diets, Inc., New Brunswick, NJ, USA) for 16 weeks. Body weight was monitored weekly, and tissues were collected for further analysis. All procedures were approved by the Yonsei University Health System Institutional Animal Care and Use Committee (2023-0021).

2.9. Statistical Analysis

Statistical analysis was performed using GraphPad Prism. For comparing two groups, statistical significance was assessed using a two-tailed unpaired Student’s t-test, while a one-way ANOVA test was used for comparisons involving multiple groups. A *p-value* of less than 0.05 was considered indicative of statistical significance.

3. RESULTS

3.1. PSMD7 is widely expressed in various tissues and upregulated in metabolic tissues under high-fat diet conditions

To assess the expression of PSMD7 in various mouse tissues, RNA was extracted from the brain, kidney, spleen, liver, heart, lung, muscle, brown adipose tissue (BAT), gonadal white adipose tissue (gWAT), and inguinal white adipose tissue (iWAT) of 16-week-old C57BL/6 wild-type mice. RT-PCR analysis revealed widespread PSMD7 expression, with particularly high levels in the heart and adipose tissue (Figure 1A).

Given the focus of this study on PSMD7's role in adipogenesis, we further investigated whether its expression is upregulated under high-fat diet (HFD) conditions. Total proteins and RNAs were extracted from the heart (Figure 1B), liver, and adipose tissues of CD and HFD-fed mice (Figure 1C–E). Western blot and RT-qPCR analyses showed that PSMD7 expression remained unchanged in the heart following HFD feeding. In contrast, its protein levels were elevated in the liver, gWAT, and iWAT, supporting PSMD7 potential involvement in lipid metabolism and adipose tissue regulation.

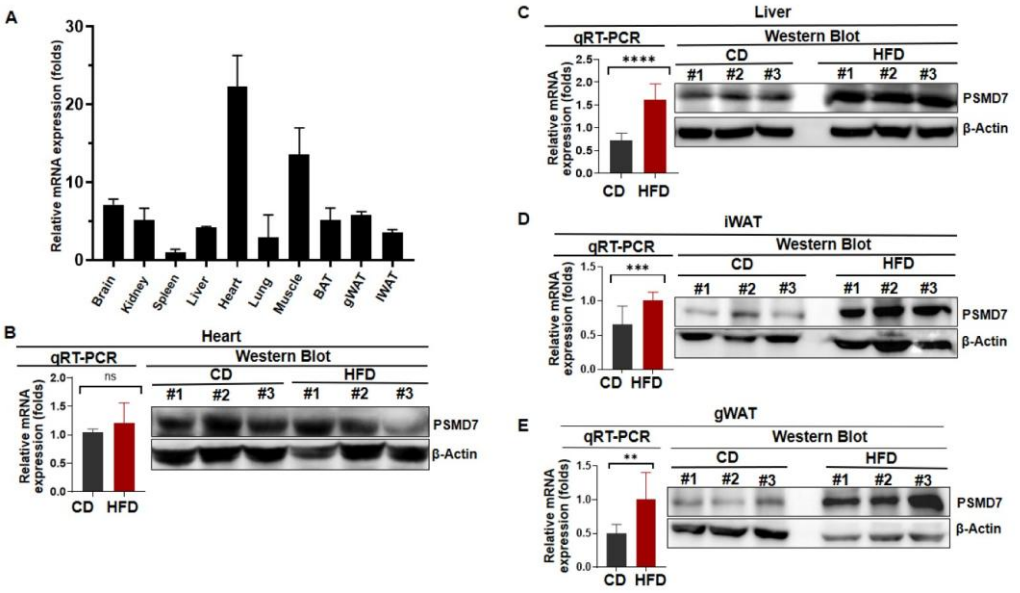

Figure 1. PSMD7 is widely expressed in most tissues and upregulated in the liver, heart, and adipose tissues of HFD-fed mice compared to CD-fed mice. (A) mRNA expression of *PSMD7* in various tissues under chow diet. **(B**) Comparison of *PSMD7* mRNA and protein expression between CD- and HFD-fed mice in the heart conditions. **(C)** Comparison of *PSMD7* mRNA and protein expression between CD- and HFD-fed mice in liver. **(D and E)** Comparison of *PSMD7* mRNA and protein expression between CD- and HFD-fed mice in iWAT, and gWAT. Data are presented as mean ± SEM (n = 3). **p < 0.05, ***p < 0.01, ****p < 0.001 vs. CD.

3.2. PSMD7 expression increased during 3T3-L1 adipocyte differentiation and was required for proper adipogenesis

To investigate the role of PSMD7 in adipogenesis, PSMD7 expression was examined during 3T3-L1 adipocyte differentiation. Upon MDI induction, both mRNA and protein levels of *PSMD7* progressively increased from day 0 to day 6, as confirmed by quantitative RT-PCR and Western blot analysis (Figure 2A).

To assess the functional importance of PSMD7, PSMD7 expression was silenced via siRNA in 3T3-L1 preadipocytes prior to differentiation. Efficient knockdown was confirmed at both transcript and protein levels (Figure 2B). By day 6 differentiation, PSMD7 knockdown cells exhibited significantly reduced expression of key adipogenic markers—C/EBPα, C/EBPβ, PPARγ, SREBP1, FASN, and FABP4—compared to control cells (Figure 2C).

Consistent with these findings, Oil Red O staining confirmed a marked decrease in lipid accumulation following PSMD7 knockdown (Figure 2D), suggesting that PSMD7 is essential for effective adipocyte differentiation.

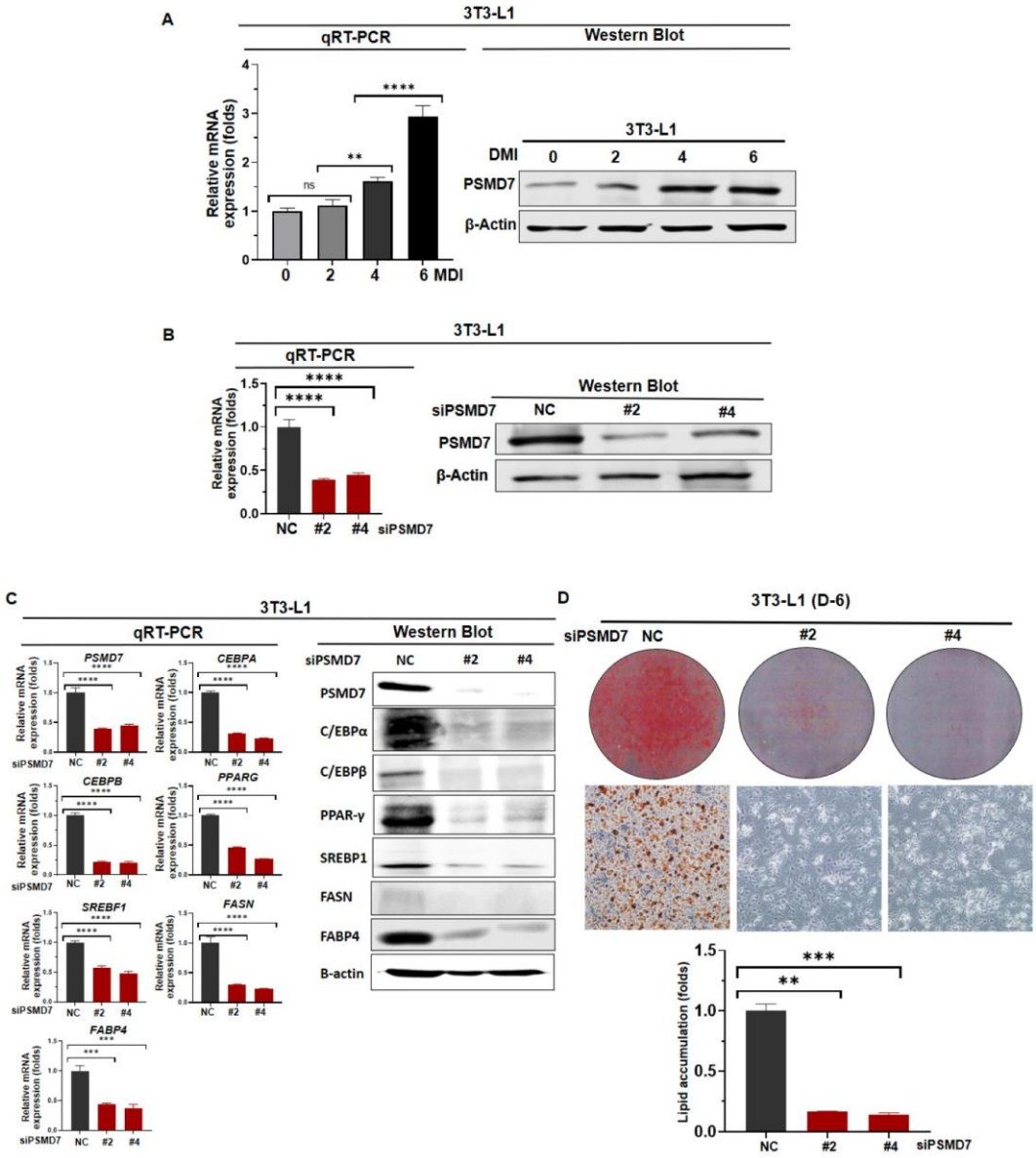

Figure 2. PSMD7 expression increased during 3T3-L1 adipocyte differentiation and was associated with adipogenic marker expression. (A) RT-qPCR and Western blot analysis of PSMD7 protein levels during adipocyte differentiation of 3T3-L1 cells, showing an increase in

PSMD7 expression from day 0 to day 6. **(B)** Validation of PSMD7 knockdown efficiency by qRT-PCR and Western blot in 3T3-L1 cells. **(C)** RT-qPCR and Western blot analysis of PSMD7 and adipogenesis markers (C/EBPα, C/EBPβ, PPARγ, SREBP1, FASN, and FABP4) at day 6 of differentiation. **(D)** Oil Red O staining of 3T3-L1 cells at day 6 to assess lipid accumulation. Data are presented as mean ± SEM (n = 3). **p < 0.05, ****p < 0.001 vs. day 0.

3.3. PSMD7 knockdown impaired adipocyte differentiation by disrupting adipogenic marker expression in 3T3-L1 cells

To evaluate the role of PSMD7 during adipogenesis, protein levels were analyzed in 3T3-L1 cells during adipocyte differentiation on days 0, 2, 4, and 6. PSMD7 levels increased progressively throughout the differentiation process, correlating with elevated expression of adipogenic markers (C/EBPα, C/EBPβ, PPARγ, SREBP1, FASN, and FABP4), as confirmed by Western blot and quantitative RT-PCR (Figure 3A–B). Quantification of Western blot bands further validated the upregulation of these proteins (Figure 3B).

Moreover, PSMD7 knockdown led to a significant reduction in the expression of key adipogenesis proteins, including C/EBPα, C/EBPβ, PPARγ, SREBP1, FASN, and FABP4, as demonstrated by both Western blot and quantitative RT-PCR analyses (Figure 3A–C). These results indicate that PSMD7 is not only upregulated during adipogenesis but is also essential for the transcriptional program driving adipocyte differentiation.

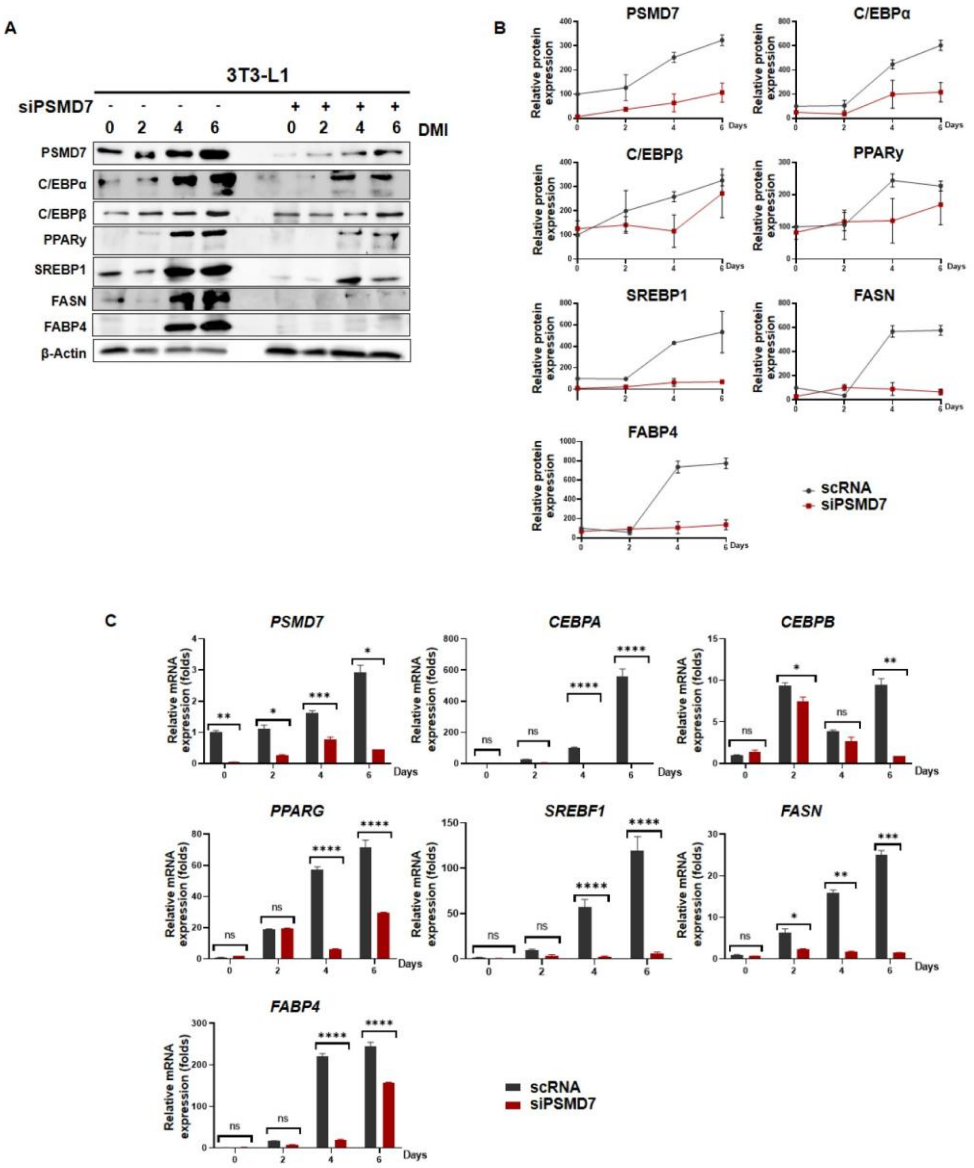

Figure 3. PSMD7 knockdown impaired adipocyte differentiation by disrupting adipogenic marker expression in 3T3-L1 cells. (A) Western blot analysis of PSMD7 expression and adipogenesis markers (C/EBPα, C/EBPβ, PPARγ, SREBP1, FASN, and FABP4) in control and PSMD7 knockdown 3T3-L1 cells during adipocyte differentiation at days 0, 2, 4, and 6. **(B)**

Quantification of Western blot bands for adipogenesis markers normalized to β-actin. **(C)** qPCR analysis of mRNA levels of adipogenic genes (*CEBPA*, *CEBPB*, *PPARG*, *SREBF1*, *FASN*, and *FABP4*) during adipocyte differentiation in control and PSMD7 knockdown cells. Data are presented as mean ± SEM (n = 3). *p < 0.05, **p < 0.01, ***p < 0.001 and ****p < 0.001 vs. day 0.

3.4. PSMD7 interacted with SREBP1 and regulated the expression of downstream adipogenic genes

To explore the molecular mechanism underlying PSMD7's role in adipogenesis, co-immunoprecipitation (Co-IP) assays were performed using HEK293T cells. The results revealed an interaction between PSMD7 and SREBP1, indicating that PSMD7 may regulate adipogenesis through its association with SREBP1 (Figure 4A).

To assess the functional effect of this interaction, the expression of SREBP1 target genes—including *FASN*, *ACC1*, *SCD1*, and *ACYL*—was analyzed by quantitative RT-qPCR in PSMD7-depleted 3T3-L1 cells at day 6 of differentiation. Knockdown of *PSMD7* significantly reduced the mRNA levels of these genes compared to control cells (Figure 4B). These results indicate that PSMD7 promotes adipogenesis by interacting with and potentially stabilizing SREBP1, thereby enhancing transcription of critical adipogenic regulators.

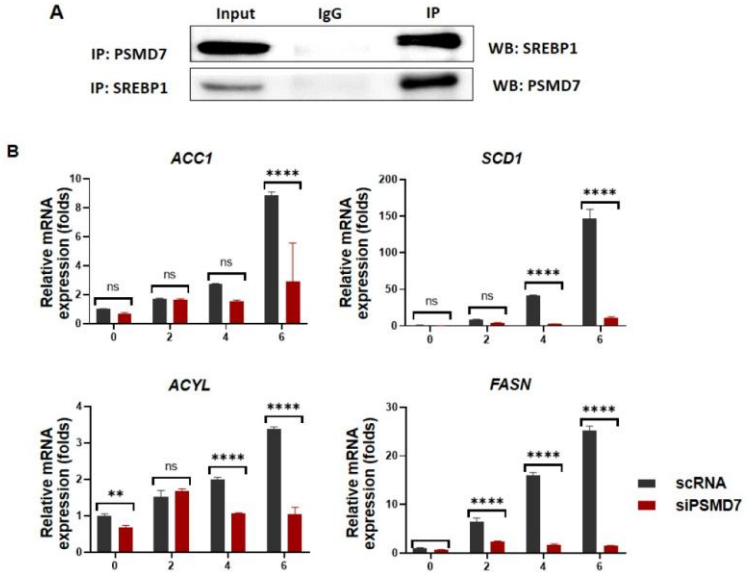

Figure 4. PSMD7 interacted with SREBP1 and regulated downstream adipogenic genes expression. (A) Co-immunoprecipitation (Co-IP) showing the interaction between PSMD7 and SREBP1 in HEK293T cells. **(B)** RT-qPCR analysis of SREBP1 target genes (*ACC1*, *SCD1*, *ACY*L, and *FASN*) in control and PSMD7 knockdown 3T3-L1 cells during adipocyte differentiation. Data are presented as mean ± SEM from three independent experiments **p < 0.001 and ****p < 0.001 vs. scRNA control.

3.5. PSMD7 stabilized SREBP1 through deubiquitination and co-localized with SREBP1 in differentiated adipocytes

To assess the role of PSMD7 in regulating SREBP1 stability, a ubiquitination assay was performed. PSMD7 knockdown resulted in increased ubiquitination of SREBP1, indicating that PSMD7 stabilizes SREBP1 by acting as a deubiquitinating enzyme (Figure 5A).

Furthermore, immunofluorescence analysis revealed partial colocalization of PSMD7 and SREBP1 in differentiated 3T3-L1 cells (Figure 5B), supporting the notion of a functional interaction between the two proteins. These findings further suggest that PSMD7 promotes adipogenesis by maintaining SREBP1 stability through deubiquitination and colocalizing with it within the cell.

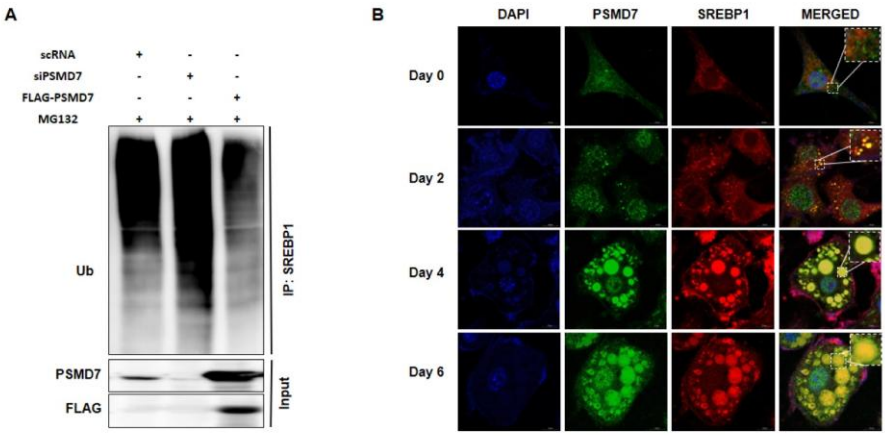

Figure 5. PSMD7 regulated SREBP1 stability through deubiquitination and colocalized with SREBP1. (A) Ubiquitination assay showing increased ubiquitinated SREBP1 in PSMD7 knockdown cells, indicating PSMD7's role in deubiquitinating SREBP1. **(B)** Immunofluorescence analysis of PSMD7 and SREBP1 showing partial colocalization during 3T3-L1 differentiation. Images are representative of three independent experiments.

3.6. PSMD7 stabilized SREBP1 by preventing proteasomal degradation.

To investigate whether PSMD7 influences SREBP1 stability through the proteasome pathway, AML12 cells were transfected with si*PSMD7* and treated with or without MG132, a proteasome inhibitor. Western blot analysis revealed that PSMD7 knockdown reduced SREBP1 protein levels, almost similar to the scrambled control, indicating enhanced protein degradation of SREBP1 (Figure 6A–B). Notably, MG132 treatment completely rescued SREBP1 protein levels in PSMD7-depleted cells, demonstrating that SREBP1 degradation is proteasome-dependent.

Consistent with this, quantitative RT-PCR analysis showed no significant changes in *SREBF1* mRNA levels between control and knockdown groups, with no significant effects of MG132 treatment (Figure 6C). These results demonstrate that PSMD7 regulates SREBP1 post-transcriptionally by protecting it from proteasomal degradation. To summarize these findings, a schematic illustration is provided (Figure 6D) showing that PSMD7 stabilizes SREBP1 by preventing ubiquitin-mediated proteasomal degradation, thereby promoting adipogenesis.

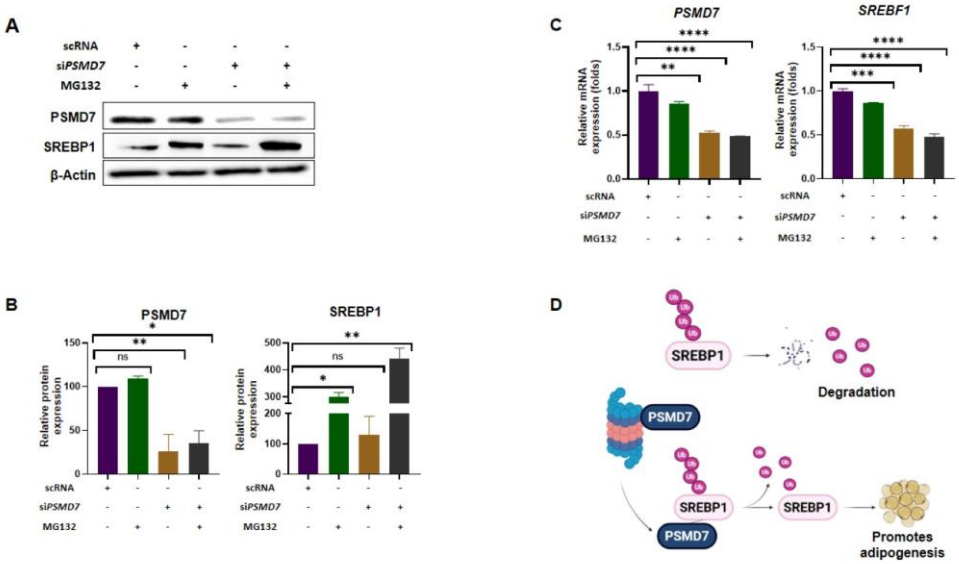

Figure 6. PSMD7 knockdown reduced SREBP1 protein levels through proteasomal degradation. (A) Western blot showing SREBP1 and PSMD7 protein levels in control and PSMD7 knockdown 3T3-L1 cells, treated with/without the proteasome inhibitor MG132 (20 μM, 8 h). **(B)**

Quantification of SREBP1 protein levels from (A). **(C)** qRT-qPCR analysis of *SREBF1* and *PSMD7* mRNA levels under the same conditions. **(D)** Schematic illustration of the proposed mechanism by which PSMD7 stabilizes SREBP1. Under normal conditions, SREBP1 undergoes polyubiquitination and proteasomal degradation, limiting its protein levels (top panel). PSMD7 prevents SREBP1 degradation by removing ubiquitin chains, thereby stabilizing SREBP1 protein and promoting adipogenesis (bottom panel). Data are presented as mean ± SEM (n = 3). Statistical significance was assessed by one-way ANOVA followed by Tukey's post hoc test. *p < 0.05, **p < 0.01,***p < 0.001, and ****p < 0.001

4. DISCUSSIONS

Metabolic diseases, particularly obesity (defined as a BMI ≥30 kg/m²), have emerged as a global public health crisis due to their escalating prevalence and association with conditions such as non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and cancer, contributing to millions of deaths annually and underscoring the need for prevention and early intervention[1–3,6].

At the cellular level, obesity is closely associated with dysregulated adipogenesis—the process by which preadipocytes differentiate into mature adipocytes—which plays a crucial role in lipid storage, energy balance, and insulin sensitivity[7–9]. This process is orchestrated by transcription factors like SREBP1, C/EBP family members, and PPARγ; their dysfunction can lead to ectopic lipid deposition and metabolic disorders[3,12–16].

In addition to transcriptional regulation, adipogenesis and fat accumulation are tightly controlled by post-translational modifications (PTMs), which influence protein activity, stability, and interactions[17,18]. Among these, ubiquitination via the ubiquitin-proteasome system (UPS) is especially crucial for maintaining cellular homeostasis, by marking misfolded or defective proteins for degradation through the 26S proteasome, composed of a 20S core and 19S regulatory particle[18–20].

Importantly, ubiquitination is a reversible process, and the deubiquitinases (DUBs), counteract this process to stabilize proteins[22,23]. Several DUBs have emerged as key regulators of lipid metabolism—such as USP1, which deubiquitinates C/EBPβ to promote adipogenesis, and USP15,

which stabilizes proteins like FABPs and perilipin to enhance lipid accumulation and contribute to NAFLD/NASH—yet the specific roles of proteasome-associated DUBs in adipogenesis remain largely unexplored[24,25].

Here, we investigated PSMD7, a JAMM/MPN domain-containing DUB and integral component of the 19S regulatory particle[26,27]. Although PSMD7 has been implicated in cancer progression (e.g., lung, bladder, and breast cancers[26,28–31], its function in metabolism was unknown. We first assessed PSMD7 expression across murine tissues, observing high levels in the heart and adipose depots (Figure 1A). Under a high-fat diet (HFD), PSMD7 protein levels increased in the liver, gonadal white adipose tissue (gWAT), and inguinal WAT (iWAT) but remained unchanged in the heart (Figure 1B–E), suggesting a potential role in lipid metabolism and adipose tissue regulation.

During 3T3-L1 adipocyte differentiation, PSMD7 expression progressively rose alongside adipogenic markers (Figure 2A). Knockdown of PSMD7 impaired lipid accumulation and downregulated adipogenic markers (Figure 2B–D), confirming its necessity for differentiation. Further analysis revealed that PSMD7 depletion reduced expression of C/EBPα, C/EBPβ, PPARγ, SREBP1, FASN, and FABP4 (Figure 3A–C), underscoring its role in the adipogenic transcriptional program.

Mechanistically, co-immunoprecipitation demonstrated that PSMD7 interacts with SREBP1, a master regulator of lipogenesis (Figure 4A). SREBP1, a member of the SREBPs family, is a master regulator of lipogenic gene expression and plays a pivotal role in adipogenesis[10,11]. The stability and activity of SREBP1 are tightly regulated by various post-translational modifications such as neddylation, phosphorylation, and ubiquitination[35,36]. Moreover, SREBP1 is known to activate a series for the synthesis of fatty acid, including fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), and stearoyl-CoA desaturase 1 (SCD-1)[37]. PSMD7 knockdown suppressed SREBP1 target genes (e.g., *FASN*, *ACC*, *ACLY*, *SCD-1*) (Figure 4B), implying that PSMD7 stabilizes SREBP1 to sustain lipid biosynthesis.

We demonstrated that PSMD7 interacts with and deubiquitinates SREBP1, enhancing the stability of SREBP1 in adipocyte differentiation (Figure 5A). Immunofluorescence confirmed their partial colocalization in adipocytes (Figure 5B), while MG132 treatment rescued SREBP1 protein levels in PSMD7-depleted cells (Figure 6A–B), confirming proteasome-dependent degradation. Notably, PSMD7 knockdown increased SREBP1 ubiquitination without altering its mRNA levels (Figure 6C), supporting a post-translational regulatory mechanism.

Our study identified PSMD7 as a novel regulator of adipogenesis by promoting SREBP1 stabilization and activity during adipocyte differentiation. To date, studies related to PSMD7 have been limited to its importance in cancer progression[26,28–32.] PSMD7 was shown to promote malignancy by deubiquitinating RAD1A in bladder cancer and RAD23B in gastric cancer[28,32]. Here, we demonstrate for the first time its critical involvement in lipid metabolism.

Beyond its canonical role as part of the 26S proteasome, our findings suggest that PSMD7 exerts a distinct, context-specific function in adipocyte differentiation. This concept aligns with emerging evidence that several proteasome subunits can operate independently. For example, the proteasome 19S lid—specifically PSMD1, but not other proteasome components—plays a critical role in mitotic bipolar spindle assembly. Upon PSMD1 depletion, the kinesin-5 motor protein KIF11, essential for spindle pole separation, undergoes aberrant ubiquitin-independent degradation, leading to monopolar spindle formation. This suggests that PSMD1, as part of the 19S lid, restrains 20S proteasome activity to ensure proper spindle assembly[38]. Similarly, PSMD14 has been reported to act independently in colorectal cancer, where it stabilizes ALK2 via deubiquitination in response to BMP6, thereby activating BMP6 signaling and promoting tumor growth and chemoresistance[39]. Together, these findings underscore a broader concept: individual proteasome subunits, including PSMD7, may have distinct, context-specific functions beyond their canonical roles in proteasomal degradation.

These findings are consistent with previous reports that PSMD1 and PSMD2 suppresses lipid synthesis by downregulating *SREBF1*[33], supporting the emerging concept that the proteasome system plays a broader role in lipid metabolism beyond their canonical roles. Consistent with its regulatory role, we found that PSMD7 expression increased progressively during 3T3-L1 adipocyte differentiation, along with key adipogenic markers such as C/EBPα, C/EBPβ, PPARγ, SREBP1, FASN, and FABP4. Importantly, the knockdown of PSMD7 impaired adipocyte differentiation, as evidenced by reduced lipid accumulation and downregulation of adipogenic gene expression. Importantly, we also observed PSMD7 upregulation in adipose tissues under high-fat diet conditions, suggesting that PSMD7-mediated SREBP1 stabilization may contribute to adipose tissue expansion or remodeling in obesity. Notably, since SREBP1 is a master regulator of lipogenesis, PSMD7-mediated stabilization of SREBP1 may enhance fatty acid synthesis, providing the lipid substrates necessary for accumulation during adipogenesis and thus supporting adipocyte differentiation.

In summary, our study reveals a novel PSMD7–SREBP1 regulatory axis essential for

adipogenesis (Figure 6D), expanding our understanding of how specific proteasome subunits interface with lipid metabolism. This work highlights the non-canonical roles of proteasome components and positions PSMD7 as a potential regulatory node in metabolic homeostasis and obesity.

5. CONCLUSION

In this study, we explored the role of the deubiquitinase PSMD7 in adipogenesis, focusing on its expression dynamics during adipocyte differentiation and its functional significance in regulating lipid accumulation. Our findings demonstrate that PSMD7 is upregulated during the course of 3T3-L1 differentiation and plays a positive regulatory role in adipogenesis.

We first observed that PSMD7 expression increases in adipose tissues under HFD-fed mouse and during the progression of 3T3-L1 adipocyte differentiation, suggesting its potential involvement in adipogenic pathways. Knockdown experiments using siRNA revealed that suppression of PSMD7 led to a marked reduction in lipid droplet formation and downregulation of key adipogenic markers, highlighting its functional contribution to adipocyte maturation.

Importantly, we demonstrate that PSMD7 exerts its pro-adipogenic effect, through the post-translational regulation of SREBP1. Specifically, PSMD7 stabilizes SREBP1 by deubiquitination, thereby preventing its proteasomal degradation. This leads to the accumulation of active SREBP1, which in turn promotes the transcription of downstream target genes involved in lipid biosynthesis and adipocyte differentiation. These findings reveal a novel PSMD7–SREBP1 regulatory axis and uncover a non-canonical function of the proteasome subunit PSMD7 as a modulator of adipogenic transcriptional programs.

Taken together, our results expand the current understanding of how components of the ubiquitin–proteasome system influence metabolic processes beyond general protein degradation. By identifying PSMD7 as a stabilizer of SREBP1 and a promoter of adipogenesis, we propose a new layer of regulation in adipocyte biology. These insights also raise the possibility that dysregulation of PSMD7 may contribute to the pathogenesis of metabolic diseases characterized by abnormal lipid storage, such as obesity, insulin resistance, and non-alcoholic fatty liver disease (NAFLD).

For future studies, it will be essential to explore the detailed molecular mechanism underlying

the PSMD7–SREBP1 interaction, and whether PSMD7 modulates overall proteasome activity during adipogenesis, or if its function is more substrate-specific. In the *in vivo* level, it is also important to assess whether modulating PSMD7 activity can affect systemic metabolic outcomes. Addressing these questions will provide deeper insight into how PSMD7 coordinates cellular signaling and protein homeostasis during adipocyte differentiation. Ultimately, understanding this axis may reveal novel targets for therapeutic strategies in metabolic disorders linked to dysregulated lipid metabolism.

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Abstract in Korean

탈유비퀴틴화 효소 PSMD7의 지방세포 조절에서의 역할

유비퀴틴–프로테아좀 시스템(ubiquitin–proteasome system, UPS)은 단백질 분해 및 대사 조절에 있어 필수적인 역할을 수행하지만, 개별 프로테아좀 소단위체의 비정형(non-canonical) 기능, 특히 지방세포 분화(adipogenesis)에서의 역할은 아직 명확히 규명되지 않았다. 본 연구에서는 26S 프로테아좀의 19S 조절 소단위체이며 탈유비퀴틴화효소(deubiquitinase, DUB)로 작용하는 PSMD7이 지방세포 분화를 조절하는 새로운 인자로 기능함을 규명하였다. PSMD7이 지방생성 인자의 안정성을 조절함으로써 비정형 기능을 수행할 수 있음을 입증하였다.

고지방식이(high-fat diet)를 투여한 마우스에서 PSMD7 발현은 간, 생식기 주변 백색지방조직(gonadal white adipose tissue, gWAT), 그리고 서혜부 백색지방조직(inguinal white adipose tissue, iWAT) 등 대사 활성이 높은 조직에서 유의하게 증가하였다. 3T3-L1 전지방세포(preadipocytes)에서는 지방분화와 함께 PSMD7 발현이 점진적으로 증가하였으며, 이는 지질 축적과도 일치하였다. PSMD7 기능을 저해한 경우, 지질 방울 형성 감소와 C/EBPα, C/EBPβ, PPARɣ, FASN, FABP4 등의 지방생성 마커 발현 저하를 통해 지방세포 분화가 저해됨을 확인하였다.

기전적으로 PSMD7은 지질생성 유전자 발현의 주요 전사인자 SREBP1과 상호작용하며 이를 디유비퀴틴화 한다. PSMD7 결핍 시 SREBP1의 유비퀴틴화가 증가하고 프로테아좀에 의한 분해가 촉진되어, 하위 표적인 FASN, ACC1, SCD1, ACYL의 발현이 감소하였다. 이 결과는 PSMD7이 SREBP1 단백질 안정성을 유지함으로써 지방세포 분화를 촉진할 수 있음을 시사한다.

종합하면, 본 연구는 지방생성을 조절하는 새로운 PSMD7–SREBP1 조절 축을 규명하였으며, 프로테아좀 소단위체의 전통적인 단백질 분해 역할을 넘어선 기능 확장을 보여준다. 이 연구는 지방세포 생물학에 대한 새로운 통찰을 제공하며, 비만 및 대사

질환 치료를 위한 잠재적 표적으로서 PSMD7의 중요성을 부각시킨다.

핵심되는 말 : PSMD7, SREBP1, 프로테아좀, 유비퀴틴화효소, 후성번역조절(post-translational modifications, PTMs), 지방세포 분화