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PML suppresses IL-6-induced STAT3 activation by interfering with STAT3 and HDAC3 interaction

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ABSTRACT

The promyelocytic leukemia protein PML acts as a tumor suppressor by forming transcription–regulatory complexes with a variety of repressor proteins. In the present study, we found that endogenous PML suppresses interleukin (IL)-6-induced gene expression as well as phosphorylation and transcriptional activation of STAT3 in hepatoma cells. We also found that PML-mediated suppression of IL-6-induced STAT3 activation by disrupting interactions between STAT3 and HDAC3. These results indicate that PML modulates IL-6-induced STAT3 activation and hepatoma cell growth by interacting with HDAC3.

1. Introduction

Interleukin (IL)-6 is a pleiotropic cytokine that regulates a variety of cellular events in vitro and in vivo [1,2]. For example, IL-6 is produced in response to infections and injuries during inflammation. Moreover, IL-6 induces terminal differentiation of B-cells into immunoglobulin-producing cells, and regulates differentiation of naïve $CD4^+$ cells into specific effector T-cell subsets, such as Th17 and regulatory T-cells [1,3,4]. In hepatocytes, IL-6 has the ability to initiate acute-phase responses to produce proteins for emergency stress signals and host defense [1,5,6].

Ligation of IL-6 to its receptor activates the Janus protein tyrosine kinase (Jak)-signal transducer and activator of transcription (STAT) pathway as well as the mitogen-activated protein kinase pathway [7,8]. The induction of various sets of IL-6-responsive genes is largely dependent on STAT3 activation [7,8]. Namely, STAT3 mediates cellular functions in many types of cells [9]; in addition, constitutive or dysregulated STAT3 expression contributes to the onset and maintenance of cancer and autoimmune diseases [10,11]. Thus, STAT3 activity is strictly regulated by multiple molecular mechanisms [12]. One mechanism is negative feedback loops by suppressor of cytokine signaling 1 (SOCS1) and SOCS3 both of which are STAT3 targets [13,14]. To terminate IL-6 signaling, SOCS1 interacts with Jak while SOCS3 binds to gp130, a signal-transducing subunit of the IL-6 receptor. The other method of regulation is via the protein inhibitor of activated STAT3 proteins, which decreases STAT-dependent transcription by inhibiting STAT3-DNA binding in the nuclei. In addition, tyrosine phosphatases, such as SH2-containing phosphatase 1 (SHP1), SHP2, and protein-tyrosine phosphatase 1B (PTP1B) in the cytoplasm as well as TCP45 (TC-PTP) in the nuclei, dephosphorylate activated STAT3 [12,15]. We have also reported that PDZ and LIM domain protein 2 (PDLIM2) acts as a nuclear E3 ligase for STAT3 [16].

Recently, an interesting relationship between STAT3 and promyelocytic leukaemia (PML) protein has been reported [17]. PML contains an RBCC motif, which comprises a RING domain, one or two B-boxes and a predicted coiled-coil region, and belongs to the TRIM protein family [18]. PML is one of components of the nuclear body, which has been implicated in many cellular functions, including apoptosis, transcriptional and translational regulation, senescence and cell proliferation [18]. Most notably, PML has the ability to suppress transcriptional activity of STAT3 [17]. Furthermore, STAT3 is aberrantly activated in PML-deficient mouse embryonic fibroblasts [19].

Therefore, it is important to determine whether PML influences on IL-6-mediated STAT3 activation. In the present study, we found

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that endogenous PML suppressed IL-6-induced gene expression and transcriptional activation of STAT3. As a mechanism, we propose a novel PML function that interferes in interactions between STAT3 and HDAC3.

2. Materials and methods

2.1. Reagents and antibodies

Human recombinant IL-6 was a kind gift from Ajinomoto (Tokyo, Japan). Trichostatin A (TSA) was purchased from Wako Chemicals (Osaka, Japan). Expression vectors for PML and HDAC3 as well as STAT3-LUC were described previously [17,20]. Anti-STAT3, anti-PML, anti-HDAC1, anti-HDAC2, anti-HDAC3, anti-PML and anti-FLAG antibodies were obtained from Santa Cruz Biotechnology (Santa Cruz, CA); anti-HA, anti-Actin antibody from Sigma–Aldrich (St. Louis, MO); anti-pSTAT3(Tyr705) and anti-pSTAT3(Ser727) antibodies from Cell Signaling Technologies (Beverly, MA).

2.2. Cell culture, transfection, siRNA and luciferase assays

A human hepatoma cell line (Hep3B) and human embryonic kidney carcinoma cell line (293T) were maintained in DMEM containing 10% FCS. Hep3B cells were transfected using jetPEI (PolyPlus-transfection, Strasbourg, France) according to the manufacturer's instructions. 293T cells were transfected using a standard calcium precipitation protocol. The siRNAs targeting human PML, HDAC1, HDAC2 and HDAC3 used in this study were as follows: PML, 5′-GGAAGGUCAUCAAGAUGGATT-3′; HDAC1, 5′-CCACAGCGAUGACUACAUUTT-3′; HDAC2, 5′-UCAGGAUUCUGUUACGUUATT-3′; HDAC3, 5′-AGAAGAUGAUCGUCUUCAATT-3′. Control siRNA was obtained from Qiagen (non-silencing; cat. no. 1022076). Luciferase activities of Hep3B cells transfected with STAT-LUC, in which the α2-macroglobulin promoter drives expression of a luciferase (LUC) reporter gene, were measured using a Dual-Luciferase Reporter Assay System (Promega, Madison, WI) according to the manufacturer's instructions.

2.3. RNA isolation, quantitative real-time PCR (qRT-PCR)

Cells were harvested and total RNAs were prepared by using TRI Reagent (Molecular Research Center, Cincinnati, OH, USA). First-strand cDNA was synthesized from 1 μg of total RNA with ReverTra Ace (TOYOBO, Osaka, Japan). Quantitative real-time PCR analysis of mRNA transcripts was carried out using a combination of a KAPA SYBR FAST qPCR master mix (KAPA Biosystems, Woburn, MA, USA) with an Mx3005P real-time PCR system (Stratagene, Santa Clara, CA, USA). Primers used for qPCR were: *PML*: 5′-CCTCTAGCTGCTGGTGGTTC-3′ (sense), 5′-AGGGAGTGGCAGCTTGAGTA-3′ (antisense), *SOCS3*: 5′-TCACCCACAGCAAGTTTCCCGC-3′ (sense), 5′-GTTGACGGTCTTCCGACAGAGATGC-3′ (antisense), *CEBPD*: 5′-ATGTACGACGACGAGAGCGCCAT-3′ (sense), 5′-CTTGTGATTGCTGTTGAAGAGGGTC-3′ (antisense), *ACTB*: 5′-TGTTACCAACTGGGACGACA-3′ (sense), 5′-GGGGTGTTGAAGGTCTCAAA-3′ (antisense).

2.4. Immunoprecipitation and immunoblotting

The immunoprecipitation and Western blotting assays were performed as described previously [21]. Briefly, the immunoprecipitates from cell lysates were resolved on SDS-PAGE and transferred to PVDF transfer membrane (PerkinElmer; Boston, MA). The filters were then immunoblotted with each antibody. Immunoreactive proteins were visualized using an enhanced chemiluminescence detection system (Millipore; Bedford, MA).

2.5. Cell growth assay

The numbers of viable Hep3B cells after the indicated treatments were measured using a WST-8 [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium, monosodium salt] assay (Cell Counting Kit-8; Wako Pure Chemicals). Briefly, 10 μl of WST-8 solution was added to the cells in each well and incubated for 2 h. The absorbances were measured at a test wavelength of 450 nm and a reference wavelength of 650 nm using a microplate reader (Bio-Rad, Hercules, CA).

2.6. Statistical analysis

The significance of differences between group means was determined by Student's t-test.

3. Results

3.1. PML suppresses IL-6-induced expression and transcriptional activation of STAT3

A human hepatoma HepB3 cell line that responds to IL-6 and is often used to analyze signals mediated by IL-6 stimulation was used in this study. With this cell line, we first tested whether ectopic expression of PML affects IL-6-mediated STAT3 activation by measuring luciferase activity for STAT3. Expression vectors for PML together with STAT3-LUC were transfected into HepB3 cells. After 24 h of transfection, the cells were stimulated with IL-6 for 12 h and harvested, and STAT3-LUC activity was determined. As shown in Fig. 1A, ectopic expression of PML down-regulated IL-6-induced STAT3 transcriptional activity in a dose-dependent manner. To further test whether a reduction in PML expression affects IL-6-induced STAT3 activation, we used siRNA to reduce endogenous PML expression. Specific siRNA for PML or a control siRNA was transfected into HepB3, followed by transfection with STAT3-LUC. Total cellular protein from the transfected cells was subjected to western blotting, which confirmed reduction of PML protein levels (Fig. 1B). PML knockdown resulted in enhancement of IL-6-induced STAT3 transcriptional activity. Furthermore, IL-6/STAT3-mediated SOCS3 and C/EBPδ mRNA expression were significantly augmented in PML-knockdown Hep3B cells (Fig. 1C). These results strongly indicate that PML suppresses IL-6/STAT3-mediated transcriptional activation and gene expression in Hep3B cells.

We next examined whether a reduction in PML expression affects IL-6-induced phosphorylation of STAT3. As shown in Fig. 1D, knockdown of PML expression increased IL-6-induced tyrosine (Tyr705)- and serine (Ser727)-phosphorylation of STAT3. In addition, reduction in PML expression increased STAT3 protein content. These results suggest that PML negatively regulates IL-6-induced STAT3 activation by influencing the phosphorylation level of STAT3.

3.2. HDAC3 regulates the suppression of IL-6-induced STAT3 activation by PML

HDACs functionally and physically interact with PML [22], and their substrates are not only histone proteins, but also the transcription factors, such as p53 and NF-κB [23,24]. Importantly, HDACs associate with and regulate STAT3 [17]. We therefore tested whether an HDAC inhibitor (TSA) affects the suppression of IL-6-induced STAT3 activation by PML in Hep3B cells. As shown in Fig. 2A, PML knockdown resulted in a significant increase of IL-6-induced SOCS3 mRNA expression. It is noteworthy that the treatment of TSA abrogated the PML knockdown-mediated increase of IL-6-induced SOCS3 mRNA expression. Therefore, HDAC activity is required for the enhancement of IL-6-induced gene expression in

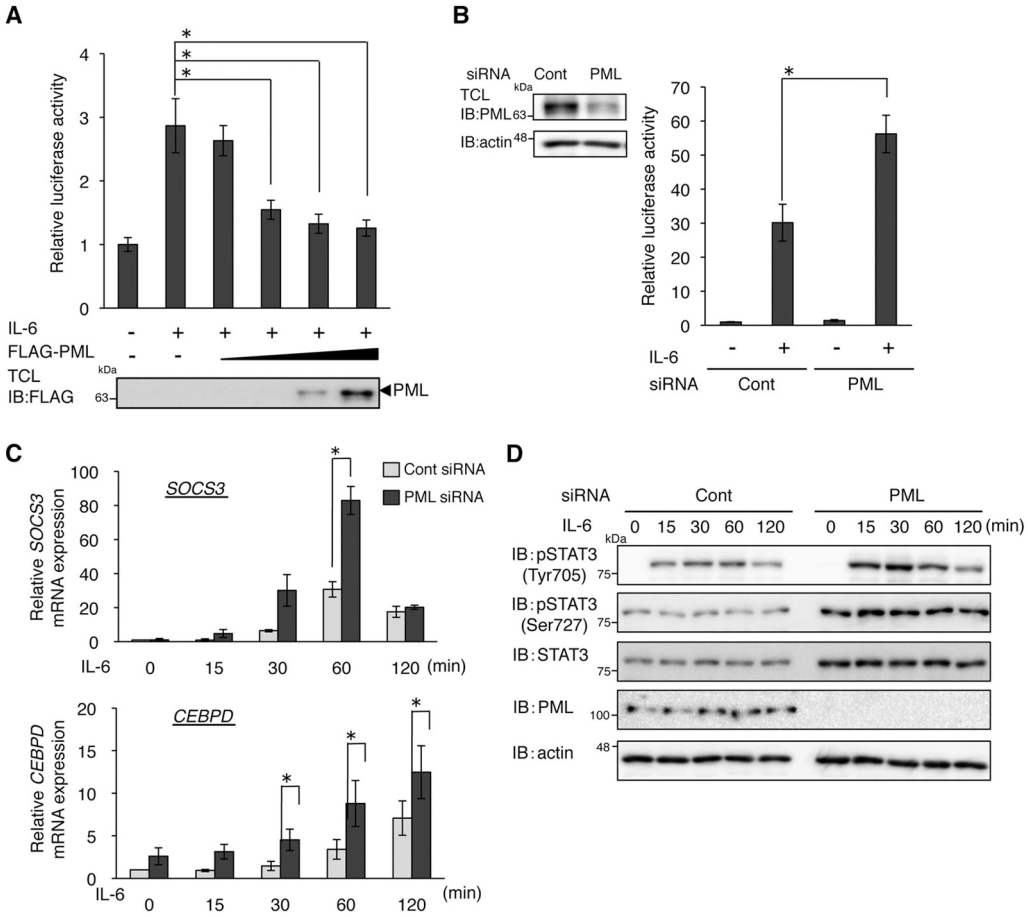

Fig. 1. PML negatively regulates IL-6-induced transactivation and phosphorylation of STAT3. (A) Hep3B cells in a 24-well plate were transfected with STAT3-LUC (100 ng) and/or the increasing amount of FLAG-PML (10, 100, 500, 1000 ng). At 24 h after transfection, cells were treated with IL-6 (5 ng/ml) for an additional 12 h. The cells were harvested and assayed for the luciferase activity. The results are indicated as fold induction of luciferase activity from triplicate experiments, and the error bars represent the SD. *$p < 0.05$. TCL (1%) was blotted with an anti-FLAG antibody. (B) Hep3B cells in a 24-well plate were transfected with control or PML siRNA (20 pmol) and then transfected with STAT3-LUC (100 ng). At 24 h after transfection, cells were treated with IL-6 (5 ng/ml) for an additional 12 h. The cells were harvested and assayed for the luciferase activity as described the above. *$p < 0.05$. TCL (1%) was blotted with anti-PML or anti-actin. (C) Hep3B cells in a 24-well plate were transfected with 20 pmol of control (gray bar) or PML siRNA (black bar). At 48 h after transfection, cells were starved of serum for 2 h and treated with IL-6 (5 ng/ml) for the indicated periods. Total RNA samples isolated from these cells were also quantified by reverse transcription and quantitative real-time PCR analysis. Data represent the levels of SOCS3 (left panel) or CEBPD (right panel) mRNA normalized to that of an ACTIN internal control and are expressed relative to the value of control siRNA-treated samples. The results are representative of three independent experiments, and the error bars represent the SD. *$p < 0.05$. (D) Hep3B cells in a 24-well plate were transfected with control or PML siRNA (20 pmol). At 48 h after transfection, cells were starved of serum for 2 h and treated with IL-6 (5 ng/ml) for the indicated periods. The cells were then lysed, and TCL (1%) was blotted with anti-pSTAT3 (Tyr705), anti-pSTAT3 (Ser727), anti-STAT3, anti-PML, or anti-actin antibody. Shown is a representative experiment, which was repeated at least three times with similar results.

PML-knockdown Hep3B cells. To further examine the involvement of HDACs in the suppression of IL-6-induced STAT3 activation by PML, we employed combination knockdown of PML and HDACs. Specific siRNA for PML or a control siRNA together with or without siRNAs for HDACs were transfected into Hep3B cells, followed by transfection with STAT3-LUC. As shown in Fig. 2B, the PML-mediated suppression of IL-6-induced STAT3 activation was significantly restored by combination knockdown of HDAC3, but not HDAC1 or HDAC2 with PML. We also tested the effects of combination knockdown of PML and HDACs on IL-6-induced SOCS3 mRNA expression; similarly, the PML-mediated suppression of IL-6-induced SOCS3 mRNA expression was significantly restored by combination knockdown of HDAC3, but not HDAC1 or HDAC2 with PML (Fig. 2C). Notably, HDAC3 knockdown did not affect IL-6-induced transcriptional activation of STAT3 and gene expression in the presence of PML. Therefore, HDAC3 is involved in the PML-mediated suppression of IL-6-induced STAT3 activation. We further examined whether combination knockdown of HDACs with PML affects IL-6-induced phosphorylation of STAT3. As shown in Fig. 2D, PML knockdown increased IL-6-induced tyrosine-phosphorylation of STAT3. Importantly, PML knockdown-induced enhanced tyrosine-phosphorylation of STAT3 was restored by combination knockdown of HDAC3, but not HDAC1 or HDAC2, with PML. These results suggest that PML negatively regulates IL-6-induced STAT3 phosphorylation through HDAC3.

3.3. PML negatively regulates physical interactions between STAT3 and HDAC3

To understand the molecular mechanisms responsible for HDAC3 involvement in the PML-mediated suppression of IL-6-induced STAT3 activation, we tested physical interactions between STAT3 with HDAC3 in the presence or absence of PML. Control siRNA- or PML siRNA-transfected 293T cells were orderly transfected with HDAC3 and/or STAT3, followed by the treatment with or without IL-6 for 30 min. Western blot analyses of the immunoprecipitates for STAT3 showed that STAT3 interacts with HDAC3 in PML siRNA-transfected, but not control siRNA-transfected, 293T cells (Fig. 3). Importantly, IL-6 stimulation enhanced this complex formation between STAT3 and HDAC3.

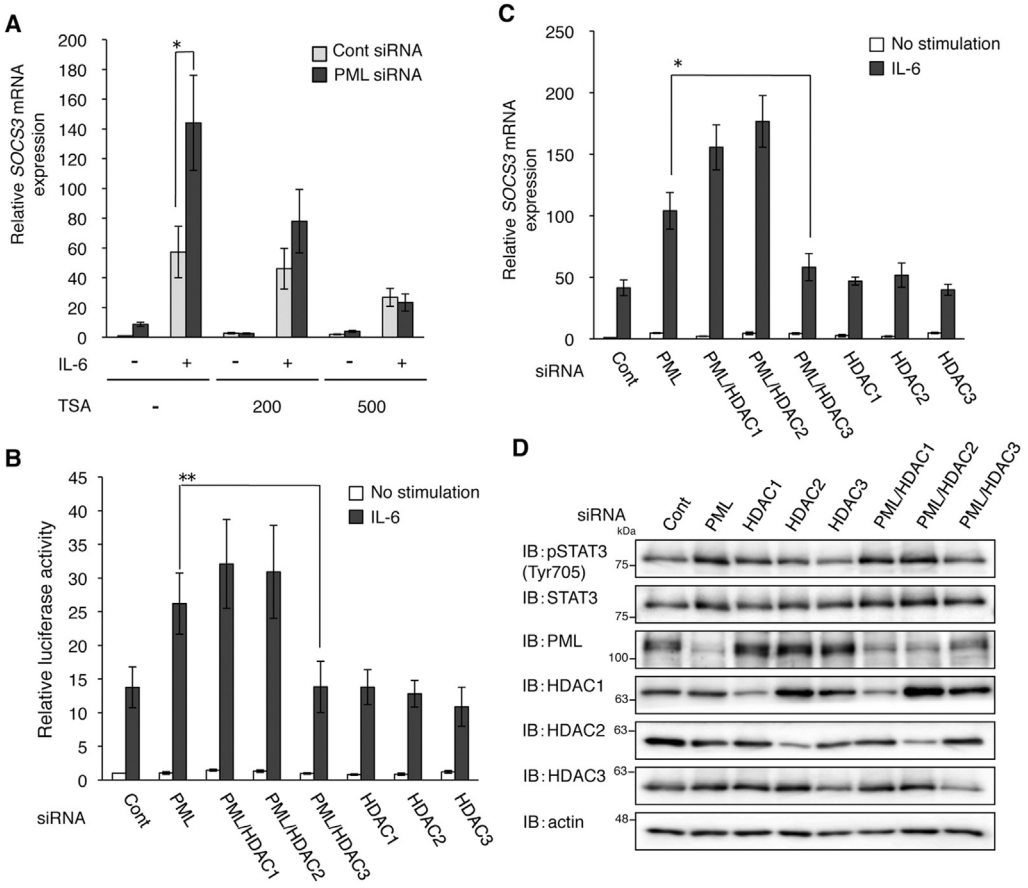

Fig. 2. HDAC3 is involved in PML-mediated inhibition of STAT3 activation after IL-6-stimulation. (A) Hep3B cells in a 24-well plate were transfected with control or PML siRNA (20 pmol). At 36 h after transfection, cells were treated or untreated with TSA (200, 500 ng/ml) for 12 h and starved of serum for 2 h, followed by IL-6 stimulation (0, 5 ng/ml) for 1 h. Total RNA samples isolated from these cells were also quantified by reverse transcription and quantitative real-time PCR analysis. Data represent the levels of SOCS3 mRNA normalized to that of an ACTIN internal control and are expressed relative to the value of control siRNA-treated samples. The results are representative of three independent experiments, and the error bars represent the SD. *$p < 0.05$. (B) Hep3B cells in a 24-well plate were transfected with control, PML, each HDAC siRNA (20 pmol) or combination of them, and then transfected with STAT3-LUC (100 ng). At 24 h after transfection, cells were treated with IL-6 (5 ng/ml) for an additional 12 h. The cells were harvested and assayed for the luciferase activity as described the above. **$p < 0.01$. (C) Hep3B cells in a 24-well plate were transfected with control, PML, each HDAC siRNA (20 pmol) or combination of them. At 48 h after transfection, cells were starved of serum for 2 h and treated with IL-6 (5 ng/ml) for 1 h. Total RNA samples isolated from these cells were also quantified by reverse transcription and quantitative real-time PCR analysis. Data represent the levels of SOCS3 or CEBPD mRNA normalized to that of an ACTIN internal control and are expressed relative to the value of control siRNA-treated samples. The results are representative of three independent experiments, and the error bars represent the SD. *$p < 0.05$. (D) Hep3B cells in a 24-well plate were transfected with control, PML, each HDAC siRNA (20 pmol) or combination of them. At 48 h after transfection, cells were starved of serum for 2 h and treated with IL-6 (5 ng/ml) for 1 h. The cells were then lysed, and TCL (1%) was blotted with anti-pSTAT3 (Tyr705), anti-STAT3, anti-PML, anti-HDAC1, anti-HDAC2, anti-HDAC3, or anti-actin antibody. Shown is a representative experiment, which was repeated at least three times with similar results.

Therefore, PML negatively regulates physical interactions between STAT3 and HDAC3.

3.4. PML negatively regulates Hep3B cell growth through HDAC3

Recent studies have demonstrated that deactivation or inhibition of STAT3 results in an enhanced chemo-sensitivity as well as a suppression of growth and metastasis of human hepatoma cells in xenografted mice [25,26]. Moreover, knockdown of STAT3 in Hep3B cells was reported to suppress cell growth [27]. Because our results indicated the involvement of PML and HDAC3 in STAT3 activity during IL-6 stimulation, we then examined whether PML or HDAC3 knockdown has any influence on cell growth. STAT3 is constitutively activated in Hep3B cells without serum starvation (data not shown). As shown in Fig. 4, PML knockdown in Hep3B cells induced a significant increase of cell growth. In addition, the PML knockdown-induced increase in Hep3B cell growth was restored by combination knockdown of HDAC3, suggesting that HDAC3 is the responsible molecule for PML knockdown-mediated enhancement of Hep3B cell growth. Therefore, the PML-HDAC3 axis may be involved in the STAT3-mediated Hep3B cell growth.

4. Discussion

In the present study, we demonstrated that endogenous PML suppresses IL-6-induced gene expression and transcriptional activation of STAT3 in Hep3B cells. The inhibitory effects of PML during IL-6 stimulation were confirmed by a decrease in STAT3 phosphorylation. As a possible mechanism, our results propose that PML-mediated suppression of IL-6-induced STAT3 activation occurs by disrupting interactions between STAT3 and HDAC3. Taken together, both PML and HDAC3 participate in IL-6/STAT3 activation in hepatoma cells.

We herein showed that PML knockdown enhanced IL-6-induced STAT3 activity in Hep3B cells. This effect was mediated by HDAC3, but not HDAC1 or HDAC2. Because PML is known to associate with HDAC1-3 in the nuclei, free HDACs may increase in the absence of PML. Among these types of HDACs, only HDAC3 has an ability to

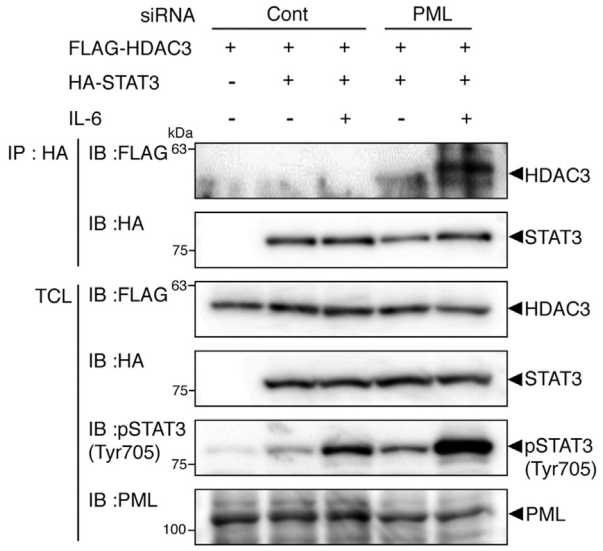

Fig. 3. PML knockdown enhances interactions between STAT3 and HDAC3. 293T cells in a 10 cm dish were transfected with control or PML siRNA (20 pmol) and then transfected with FLAG-tagged HDAC3 (10 μg) together with or without HA-tagged STAT3 (10 μg). At 24 h after transfection, cells were treated with IL-6 (5 ng/ml) for an additional 30 min. The cells were harvested and lysed, immunoprecipitated with anti-HA, and blotted with anti-FLAG or anti-HA antibody. TCL (1%) was blotted with anti-FLAG, anti-HA, anti-pSTAT3(Tyr705), or anti-PML antibody.

move from the nuclei into the cytoplasm [28]. This might be a reason for the selective involvement of HDAC3, although it is possible that HDAC3 has specific effects on STAT3 activity.

In MCF-7 and HeLa cells, histone acetyltransferase p300 induces acetylation of STAT3 at Lys685, which is critical for STAT3 to form a stable dimer required for transcriptional activation of STAT3 [29]. Moreover, HDAC3 strongly interacts with and deacetylates STAT3 at Lys685. In HeLa cells, HDAC3 inhibition enhances LIF-stimulated phosphorylation of STAT3 at Ser727 [20]. These findings indicate that HDAC3 negatively regulates the phosphorylation and transcriptional activation of STATs in some types of cells. However, recent studies have demonstrated the positive regulation of STAT3 activation by HDAC3. In NIH3T3 cells, the HDAC inhibitor TSA inhibits PDGF-induced transcriptional activation of STAT3 [30]. HDAC inhibition increased acetylation of STAT3 at Lys685 and abolished

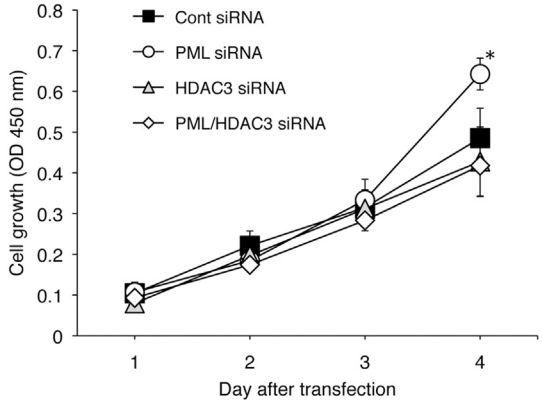

Fig. 4. PML knockdown influences cell growth in Hep3B cells. Hep3B cells in a 6-well plate were transfected with control, PML HDAC3 or PML and HDAC3 siRNA (20 pmol). At 24 h after transfection, siRNA-transfected cells were harvested and seeded into 96-well plates (3×10^3/well). At the indicated time point, viable cells were evaluated by Cell Counting Kit-8. Shown is a representative experiment, which was repeated at least three times with similar results, and the error bars represent the SD. $^*p < 0.05$.

phosphorylation of STAT3 at Tyr705 with minimal effect on STAT3 at Ser727 in diffuse large B-cell lymphoma cells [31]. Furthermore, HDAC3 knockdown also increased acetylation of STAT3 at Lys685 and decreased phosphorylation of STAT3 at Tyr705, resulting in survival reduction of phospho-STAT3 positive diffuse large B-cell lymphoma cells. Similarly, HDAC3 knockdown or the HDAC3 inhibitor BG45 down-regulates phosphorylation of STAT3 at both Tyr705 and Ser727 residues and induces cell growth inhibition via apoptosis in multiple myeloma cells [32]. Moreover, HDAC3 inhibition also induces hyperacetylation of STAT3 at Lys685 in these cells. Therefore, HDAC3 is now believed to be a positive regulator of STAT3 in some cell types by influencing phosphorylation and acetylation of STAT3.

In Hep3B cells, we showed that HDAC3 positively regulated the phosphorylation of both Tyr705 and Ser727 of STAT3 during IL-6 stimulation. As mentioned above, positive and negative effects of HDAC3 on STAT3 activity have been reported [29,31,32], and our results in Hep3B cells are similar to reports describing positive regulation. This difference (positive vs negative regulation) may be dependent on types of cells and stimuli. Alternatively, different experimental condition might be another reason for this difference. In our previous reports, we showed that HDAC3 recruits the protein phosphatase PP2A to STAT3 in HeLa cells [20] and that KAP1 effectively bridges STAT3 and HDAC3 in 293T cells [33]. In addition, several molecules, such as SHP1, SHP2, PTP1B, and TCP45, have been reported to regulate STAT3 phosphorylation [12,15]. Thus, cellular circumstances, including expression levels of these proteins, may determine the involvement of HDAC3 in STAT3 activity. Further analysis will clarify this issue.

Based on the present data, we propose PML as a novel player that interferes in interactions between STAT3 and HDAC3 to regulate IL-6/STAT3-mediated signaling in Hep3B cells. Therefore, reduced PML expression is likely to increase STAT3 activation and cell growth in hepatoma cells. Importantly, PML expression is frequently lost in a variety of human cancers [34], and this may be one of the underlying reasons for constitutive activation/phosphorylation of STAT3 in many types of human cancers. Our findings suggest that HDAC3 is a possible target for novel therapeutic strategies aimed at treating PML-decreased and phospho-STAT3-positive hepatomas or other cancers.

Conflict of interest

The authors declare that there are no conflicts of interest.

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