Phosphorylation of the Histone Deacetylase 7 Modulates Its Stability and Association with 14-3-3 Proteins*

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Class II histone deacetylases (HDACs) play a role in myogenesis and inhibit transcriptional activation by myocyte enhancer factors 2. A distinct feature of class II HDACs is their ability to shuttle between the nucleus and the cytoplasm in a cell type- and signal-dependent manner. We demonstrate here that treatment with the 26S proteasome inhibitors, MG132 and ALLN, leads to detection of ubiquitinated HDAC7 and causes accumulation of cytoplasmic HDAC7. We also show that treatment with calyculin A, a protein phosphatase inhibitor, leads to a marked increase of HDAC7 but not HDAC5. The increase in HDAC7 is accompanied by enhanced interaction between 14-3-3 proteins and HDAC7. HDAC7 mutations that prevent the interaction with 14-3-3 proteins also block calyculin A-mediated stabilization. Expression of constitutively active calcium/calmodulin-dependent kinase I stabilizes HDAC7 and causes an increased association between HDAC7 and 14-3-3. Together, our results suggest that calcium/calmodulin-dependent kinase I-mediated phosphorylation of HDAC7 acts, in part, to promote association of HDAC7 with 14-3-3 and stabilizes HDAC7.

Acetylation and deacetylation of histone tails are critical mechanisms regulating gene expression. Acetylation of histone tails has been suggested to play a role in remodeling chromatin and to serve as signals for specific recognition by transcription factors and chromatin remodeling proteins (1–4). Histone acetylation and deacetylation are catalyzed by two groups of enzymes, histone acetyltransferases and histone deacetylases (HDACs)

1 The abbreviations used are: HDAC, histone deacetylase; E1, ubiquitin-activating enzyme; E2, ubiquitin carrier protein; E3, ubiquitin-protein isopeptide ligase; Ub, ubiquitin; HA, hemagglutinin; ALLN, N-acetyl-leucyl-leucyl-norleucinal; GST, glutathione S-transferase.

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receptors have been shown to be targets of ubiquitin-mediated proteolysis (34–38). Ubiquitination is catalyzed by a set of enzymes, E1, E2, and E3, via three sequential steps (39, 40). Ubiquitin is first activated by a single ubiquitin-activating enzyme, E1. Subsequently, one of several E2 enzymes (ubiquitin-conjugating proteins) transfers ubiquitin from E1 to a member of the ubiquitin-protein ligase family, E3, that is responsible for covalent attachment of ubiquitin to lysine residues in substrate proteins. Ubiquitin-marked proteins are then recognized by the 26 S proteosome and degraded. Regulation of protein degradation by the proteosome pathway depends primarily on the ubiquitination of targeted proteins. Recent studies have demonstrated the phosphorylation of substrate proteins implicated in ubiquitin (Ub)-mediated proteolysis (41–43).

In this study, we demonstrate that cytoplasmic HDAC7 is a target of ubiquitin-mediated proteolysis. Increased phosphorylation leads to a marked increase of endogenous and transfected HDAC7. This phosphorylation-dependent activity requires the N-terminal conserved serine residues of HDAC7. We show that phosphorylation promotes association of endogenous HDAC7 with 14-3-3 in the cytoplasm. Co-expression of a constitutively active CaMK I promotes HDAC7/14-3-3 interactions and results in an increase of HDAC7. Our data suggest a concerted regulation of HDAC7 activity by phosphorylation-mediated nuclear export and ubiquitin-regulated proteolysis.

MATERIALS AND METHODS

Plasmid Construction and Reagents—The plasmids pCMX, pCMX-mHDAC7 (WT)-HA, and pCMX-1F-14-3-3 were constructed by PCR of HDAC7 or SORC-CaMK I expression vector (a kind gift from Dr. Anthony Means) and subcloned into pCMX-1F vector. HA-Ub +1 expression plasmids were kindly provided by Dr. Rajay Pimplikar. MG132 and calyculin A were purchased from Sigma. ALLN was from Calbiochem. Anti-HDAC4, -5, and -7 antibodies were purchased from Santa Cruz Biotechnology. Anti-FLAG M2-agarose beads and anti-HA agarose beads were from Sigma and Roche Applied Science, respectively. Anti-FLAG M2-agarose beads and anti-HA agarose beads were from Sigma and Santa Cruz Biotechnology, Inc. (Santa Cruz, CA), respectively. Anti-14-3-3, anti-ubiquitin, anti-glyceraldehyde-3-phosphate dehydrogenase, anti-lamin B, and anti-β-actin were purchased from Santa Cruz Biotechnology.

**Commmunoprecipitation—** For co-immunoprecipitations, HEK293 cells on 10 × 10-cm plates were transfected with 10 μg of the appropriate plasmids using either CaPO4 or liposomes. Cells were harvested after 48 h, washed with 1× PBS, and resuspended in resuspension buffer (1 ml of 50 mM Tris, pH 8.0, 150 mM NaCl, 10% glycerol, 0.5% Triton X-100, 1 mM phenylmethylsulfonyl fluoride, and a mixture of protease inhibitors [Roche Applied Science]). Cells were sonicated and cleared by centrifugation for 15 min at 14,000 rpm. The supernatants were kept as whole cell extract. Alternatively, pre-clearing by incubation with protein A/G-agarose (Santa Cruz Biotechnology), immunoprecipitations were carried out using M2-agarose beads (Sigma) for 2 h at 4°C. After washing four times with resuspension buffer, samples were boiled in SDS loading buffer, separated on SDS-PAGE gels, transferred to nitrocellulose membranes, and probed with the appropriate antibodies. For in vitro ubiquitination of HDAC7, after treatment by 20 S proteosome inhibitors, HEK293 cells were lysed in radioimmune precipitation buffer. Co-immunoprecipitation was also performed in radioimmune precipitation buffer.

**Fractionation of Nuclear and Cytoplasmic Extracts—** Nuclear and cytoplasmic fractions were prepared according to Ref. 44. Briefly, cell-free extracts were lysed in hypotonic lysis buffer (20 mM HEPES, pH 7.8, 0.2 mM EDTA, 20% glycerol, 10 mM NaCl, 1.5 mM MgCl2, 0.1% Triton X-100, 25 mM NaF, 25 mM β-glycerophosphate, 1 mM dithiothreitol with added protease inhibitors) for 30 min on ice. Nuclei were pelleted by centrifugation at 800 g for 3 min. The resulting supernatant was centrifuged at 14,000 rpm for 15 min at 4°C to yield cytoplasmic extracts. The pellet nuclei were washed once with lysis buffer and resuspended in lysis buffer, briefly sonicated, and centrifuged at 17,000 × g for 15 min at 4°C. The supernatants were kept as nuclear extracts. Immunoprecipitation was carried out using 14-3-3 antibodies followed by SDS-PAGE and Western blot analyses probed with 14-3-3 and purified HDAC7 antibodies.

**Inhibitor Studies—** For endogenous proteins, subconfluent HEK293 cells were treated with 10 μM calyculin A for 1 h followed by cell extract preparation or fractionation. Transfected cells were treated with 20 μM calyculin A for 1 h before harvest, and the expression level of transfected proteins was examined. HEK293 cells or HEK293 cells transfected with expression vectors expressing HA-HDAC7 were treated with 20 μM MG132 or 25 μM ALLN 48 h posttransfection for the indicated time before harvesting cells.

**RESULTS**

**Inhibitors of 26 S Proteosome Stabilize Cytoplasmic HDAC7—** To determine whether class II HDACs are subject to proteosome-mediated degradation, HEK293 cells were treated with ALLN and MG132, inhibitors of the 26 S proteosome. Cells were harvested after 2–4 h of treatment, and extracts were subjected to Western blot analyses with antibodies against class II HDACs (Fig. 2). We found that all three HDACs were stabilized by ALLN and MG132, although the degree of stabilization differed. The stabilization of HDAC4 and -5 was modest but reproducible. In contrast, stabilization of HDAC7 was more dramatic. Subcellular fractions were prepared for Western blot analyses probed with anti-HDAC7 antibodies. We found that MG132 caused an accumulation of HDAC7 in the

**Ub-mediated Proteolysis of HDAC7**

**Specificities of class II HDAC antibodies.** A, HA-HDAC4, -5, and -7 were in vitro transcribed and translated (TNT). Western blots of TNT class II HDACs were probed with anti-HA (lanes 1–3), anti-HDAC4 (lanes 4–6), anti-HDAC5 (lanes 7–9), and anti-HDAC7 (lanes 10–12) antibodies. B, specificity of HDAC7 antibodies. A rabbit polyclonal anti-HDAC7 antiserum was raised against GST-HDAC7(2–254) and affinity-purified. Purified HDAC7 antibodies were used to probe HEK293 whole cell extracts (lane 1). In vitro transcribed and translated (TNT) HA-HDAC4, -5, and -7 were resolved on SDS-PAGE, followed by Western blot analyses probed with anti-HDAC7 (lanes 2–4) antibodies.
the average of two Western blots.

lized by 26 S proteosome.

Cyttoplasmic HDAC7 is stabilized by 26 S proteasome. A, cytoplasmic HDAC7 is stabilized by MG132. Nuclear (N) and cytoplasmic (C) fractions were prepared, fractionated on SDS-PAGE, and analyzed by Western blotting probed with anti-HDAC7. Anti-actin and anti-lamin B were used as cytoplasmic and nuclear markers, respectively. B, transfected HA-HDAC7 is stabilized by MG132. Whole cell extracts were prepared, and Western blots were probed with anti-HA (upper panel) and anti-glyceraldehyde-3-phosphate dehydrogenase (G3PDH) (lower panel) antibodies, respectively. Glyceraldehyde-3-phosphate dehydrogenase was used as a loading control. C, cytoplasmic HA-HDAC7 in transfected cells is stabilized by MG132. Western blots were performed as in A except that fractions were prepared from cells transfected with HA-HDAC7 (B). As a control, HDAC7 (S-A), which was shown to constitutively localize in the nucleus, was included for fractionation (lanes 9 and 10).

cytoplasmic but not the nuclear fraction (Fig. 3A). Additionally, we found that whole cell extracts and the cytoplasmic fraction of HEK293 cells transfected with a plasmid encoding HA-HDAC7 contained increased amounts of HA-HDAC7 in the presence of MG132 (Fig. 3, B and C). These results indicate that class II HDACs can be stabilized by 26 S proteasome inhibitors and that proteolysis of both endogenous and transfected HDAC7 is mediated, in part, by the 26 S proteasome.

Ectopic Expression of Ubiquitin Decreases the Expression of HDAC7—To test whether Ub has a role in proteasomal degradation of HDAC7, we tested the ubiquitination of this protein. Whole cell extracts were prepared from cells treated with ALLN or MG132 followed by immunoprecipitation with anti-HDAC7 antibodies and Western blot analysis using anti-Ub antibodies. As shown in Fig. 4A, immunoprecipitated HDAC7 proteins were ubiquitinated in both ALLN-treated (lane 4) and MG132-treated cells (lanes 5 and 6). In contrast, immunoprecipitation in the absence of anti-HDAC7 antibodies did not yield ubiquitination signals (lanes 1 and 2). Furthermore, co-transfection of a Ub frameshift mutant, Ub +1 (which blocks 26 S proteasome activity) (45) leads to a dramatic increase in HDAC7 (Fig. 4B) and the detection of a ubiquitinated protein whose size was similar to that of FLAG-HDAC7 (Fig. 4C, left panel, lane 4). Immunoprecipitation of Ub +1-containing lysates with M2 (anti-FLAG antibodies)-agarose beads followed by blotting with anti-Ub antibodies demonstrated that FLAG-HDAC7 was ubiquitinated (right panel, lane 4).

To further demonstrate that HDAC7 is capable of being ubiquitinated in vivo, HA-Ub and FLAG-HDAC7 expression plasmids were co-transfected into HEK293 cells, and IP was carried out using M2-agarose beads. Fig. 5 shows the expression of ubiquitinated cellular proteins (upper panel) and FLAG-HDAC7 (bottom panel). MG132 treatment led to an accumulation of ubiquitinated cellular proteins and an increased level of FLAG-HDAC7. M2 beads co-precipitate FLG-HDAC7 species that can be detected by anti-HA antibodies (lane 4). These co-precipitated species represent FLAG-HDAC7 species covalently linked to Ub, indicating that HDAC7 is a target of the ubiquitination machinery. The addition of MG132, which inhibits proteosomal degradation of HDAC7, leads to an accumulation of ubiquitinated HDAC7 (lanes 5 and 6). Together, our results strongly suggest that HDAC7 is subjected to Ub-mediated proteolysis.

Phosphorylation Regulates the Steady State Level of HDAC7 and Promotes HDAC7/14-3-3 Association—Ubiquitination is not the only effector of protein degradation. Phosphorylation has been implicated in the regulation of protein stability in several systems (41). To investigate whether phosphorylation
might control the steady state level of HDAC7, we conducted inhibitor studies using calyculin A, an inhibitor of serine and threonine phosphoprotein phosphatases. As shown in Fig. 6A, calyculin A treatment of HEK293 cells led to a marked increase of HDAC7 but not HDAC5 or β-actin. Cell fractionation demonstrated that cytoplasmic HDAC7 was the target of phosphorylation-mediated stabilization (Fig. 6B, lanes 1 and 3). Since 14-3-3 proteins associate with phosphoserine/phosphothreonine-containing motifs in HDAC7, we tested whether hyperphosphorylation induced by calyculin A can promote HDAC7/14-3-3 interaction. Immunoprecipitation experiments were conducted and showed that the increase of HDAC7 correlated with an enhancement of HDAC7/14-3-3 association (Fig. 6C, compare lanes 1 and 3). Similar to endogenous HDAC7, transfected FLAG-tagged HDAC7 was also stabilized by calyculin A (Fig. 6D, lane 2). However, the S178A/S344A/S479A HDAC7...
mediate stabilization of HDAC7 through distinct pathways. These results suggest that MG132 and calyculin A—

since ele-

14-3-3 Association

CaMK I (bottom panel, compare lanes 1 and 3) associates with higher levels of 14-3-3 proteins in the presence of MG132 (lane 2), calyculin A (lane 3), or their combination (lane 4). We found that treatment of both MG132 and calyculin A had an additive effect on the expression of FLAG-HDAC7 (lane 4). Immunoprecipitation was used to examine whether FLAG-HDAC7 is ubiquitinated in the presence of MG132, calyculin A, or their combination (Fig. 7B, upper panel). Whereas MG132 treatment resulted in significant accumulation of ubiquitinated HDAC7 (Fig. 7B, lower panel, lane 2), calyculin A treatment only had a slight effect (lane 3). These results suggest that MG132 and calyculin A mediate stabilization of HDAC7 through distinct pathways.

Co-expression of CaMK I Increases Steady State Level of HDAC7 and Promotes HDAC7/14-3-3 Association—Since elevated phosphorylation up-regulates the steady state level of HDAC7 and because CaMK I is responsible for phosphorylation of the conserved serine residues of HDAC7 (12), we tested whether CaMK I was capable of regulating HDAC7 stability. As shown in Fig. 8A, ectopic expression of CaMK I or 14-3-3e increased HDAC7 accumulation (top panel, lanes 2 and 3). Furthermore, co-expression of CaMK I and 14-3-3e results in an additive of accumulated HDAC7 (lane 4). Immunoprecipitation with anti-HA antibodies demonstrated that HDAC7 associates with higher levels of 14-3-3 proteins in the presence of CaMK I (bottom panel, compare lanes 6 and 8), suggesting that CaMK I promoted HDAC7/14-3-3 association (lanes 6 and 8). GST pull-down assays were carried out to examine the association between 14-3-3 and HDAC7 (Fig. 8B). GST-14-3-3e interacted more strongly with HDAC7 co-transfected with CaMK I. These data suggest that phosphorylation-dependent stabilization of HDAC7 is partly mediated by activation of CaMK I signaling, which in turn promotes HDAC7 association with 14-3-3.

**DISCUSSION**

Both class I and class II HDACs have been shown to be targets of protein modifications such as sumoylation and ubiquitination. Sumoylation has been implicated in modulating HDAC1-mediated transcriptional repression (46, 47) and plays a role in nuclear import of HDAC4 (48). Furthermore, HDAC6 is implicated in the control of protein ubiquitination (49). In this study, we have shown that the steady state levels of HDAC4, -5, and -7 are sensitive to MG132 and ALLN, inhibitors of the 26 S proteosome. We further demonstrated that HDAC7 was subject to Ub-mediated proteolysis and that this

**FIG. 6.** Phosphorylation regulates HDAC7 stability. A, HEK293 cells were treated with calyculin A for 1 h. Total cell extracts were isolated, and SDS-PAGE was conducted for Western blot analyses probed with HDAC7 or HDAC5 antibodies. As a control, anti-β-actin antibodies were used to normalize the loading. B, calyculin A causes accumulation of endogenous cytoplasmic HDAC7; same as A, except that cytoplasmic (C) and nuclear fractions (N) were used. C, calyculin A enhances association between HDAC7 and 14-3-3 proteins. Cytoplasmic fractions (C, lanes 1 and 3) were used for immunoprecipitation with 14-3-3 antibodies (lanes 1 and 3) and probed with HDAC7 (top) or 14-3-3 antibodies (bottom). Beads alone were used as controls (lanes 2 and 4). D, conserved serine residues are critical for calyculin A-mediated stabilization of HDAC7; same as A except that extracts were prepared from cells transfected with wild-type or serine mutant (HDAC7 S178A/S344A/S479A).

**FIG. 7.** MG132 and calyculin A inhibit distinct pathways involved in HDAC7 degradation. A, MG132 and calyculin A additively stabilize HDAC7. Cells transfected with FLAG-HDAC7 were treated with 20 μM MG132 (lane 2), 20 μM calyculin (lane 3), or both (lane 4) for 2 h. B, calyculin A-mediated stabilization of HDAC7 does not accumulate ubiquitinated HDAC7. Immunoprecipitation was carried out with the extracts described in the legend to Fig. 5 using M2-agarose beads followed by SDS-PAGE and Western blot analyses probed with anti-ubiquitin antibodies.
proteolysis was modulated by phosphorylation of HDAC7. Our results are the first to demonstrate that phosphorylation regulates HDAC protein stability.

We noted that the degrees of MG132-mediated stabilization of class II HDACs were quite different. In contrast to HDAC7, the levels of HDAC4 and HDAC5 were only moderately elevated by MG132. We speculate that this observation may be related to the subcellular distribution of class II HDACs. Indeed, we previously reported that the subcellular localizations of HDAC5 and HDAC7 are different and are used to determine which band is HDAC5 or CaMK I. The effect of CaMK I on the association of 14-3-3 and HDAC7 was examined by immunoprecipitation (IP) experiments using anti-HA antibodies (right panel). The immune pellets were subject to Western blot analyses (IB) probed with anti-HA (HDAC7) and anti-FLAG (14-3-3) antibodies, respectively. B, in vitro GST pull-down assays were used to examine the interaction between 14-3-3 and HDAC7. Note that an equal concentration of HDAC7 (lanes 1 and 2) was loaded for pull-down assays.

FIG. 8. CaMK I up-regulates the steady state levels of HDAC7 and promotes HDAC7 and 14-3-3 association. A, HA-HDAC7 expression plasmid was co-transfected with an expression plasmid of FLAG-14-3-3, FLAG-CaMK I, or both into HEK293 cells. Whole cell extracts were prepared and resolved on SDS-PAGE followed by Western blot analysis probed with anti-HA (HDAC7) or anti-FLAG (14-3-3) and CaMK I antibodies (left panel). The sizes of 14-3-3e and CaMK I are different and are used to determine which band is 14-3-3e or CaMK I. The effect of CaMK I on the association of 14-3-3 and HDAC7 was examined by immunoprecipitation (IP) experiments using anti-HA antibodies (right panel). The immune pellets were subject to Western blot analysis (IB) probed with anti-HA (HDAC7) and anti-FLAG (14-3-3) antibodies, respectively. B, in vitro GST pull-down assays were used to examine the interaction between 14-3-3 and HDAC7. Note that an equal concentration of HDAC7 (lanes 1 and 2) was loaded for pull-down assays.

FIG. 9. Models for phosphorylation-dependent stabilization of HDAC7. Two mechanisms may account for phosphorylation-dependent stabilization of HDAC7. A, hyperphosphorylated HDAC7 is a preferred substrate for Ub-mediated proteolysis. However, 14-3-3 proteins bind phosphorylated HDAC7 on Ser178, Ser344, and Ser479 and inhibit E3 ligase recognition and/or ubiquitination of HDAC7. B, alternatively, hypophosphorylated HDAC7 is a preferred substrate for Ub-mediated proteolysis. Phosphorylation of HDAC7 by CaMK I or blocking phosphatase activity by calyculin A treatment enhanced 14-3-3 binding. In both models, binding of 14-3-3 with HDAC7 can also block nuclear import of HDAC7.
stable complexes with 14-3-3 in the cytoplasm (Fig. 4). Interestingly, a recent paper suggested that 14-3-3 is involved in stabilization of p53 by blocking Mdm2 binding (51).

Phosphorylation is associated with the stability of several proteins. The peptidyl-prolyl cis-trans-isomerase, Pin1, binds a phosphorylated serine/threonine-containing motif with a distinct specificity (followed by a proline residue, (S/T)P) (52). Interestingly, Pin1 is able to regulate stability of its interacting partners (53). Recently, it was shown that Pin1 potentiates p53 stabilization of p53 by blocking Mdm2 binding (51).

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