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Regulation of the HIF-1α stability by histone deacetylases

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Received October 10, 2006; Accepted November 14, 2006

Abstract. Histone deacetylase inhibitors (HDACIs) are currently in clinical trials partly due to their potent anti-angiogenic effects. However, the detailed mechanism of their action is unclear. Here, we observed that several HDACIs (TSA, SB, Apicidin, and VPA) dramatically decreased HIF-1α protein level and transcriptional activity of HIF-1 in human and mouse tumor cell lines. Furthermore, class I HDACs, HDAC1 and 3 enhanced HIF-1α stability and HIF-1 trans-activation function in hypoxic conditions. In addition, immunoprecipitation and *in vitro* binding assays revealed that HDAC1 and 3 directly bind to the oxygen-dependent degradation domain of HIF-1α. Collectively, these results suggest that HDAC1 and 3 are considered as a positive regulator of HIF-1α stability via direct interaction and may play an important role in HIF-1-induced tumor angiogenesis.

Introduction

HDACs are enzymatic components of multi-protein complexes that are recruited by transcription factors to specific DNA regulatory sequences. They remove acetyl residues from nucleosomal histones and other substrates leading to chromatin condensation and gene repression (1-5). HDACs are divided into three classes: class I HDACs (HDACs 1-3, and 8) are similar to the yeast RPD3 protein and mainly localize to the nucleus (6-8); class II HDACs (HDACs 4-7, 9 and 10) are homologous to the yeast HDA1 protein and are detected in both nucleus and cytoplasm (9-17); and class III HDACs form a structurally distinct class of NAD-dependent enzymes that are similar to the yeast SIR2 proteins (18,19). Major functions of HDACs are to control gene expression, transport ubiquitinated protein aggregates, and deacetylate proteins (20-22).

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Key words: histone deacetylase, histone deacetylase inhibitor, HIF-1α

Global suppression of HDAC activity by chemical inhibitors generally raises cell cycle arrest and may affect cell proliferation and differentiation (23,24). Specific HDACIs have been used to explain HDAC function and suggested as a therapy for some types of cancers (25). Consequently, they have been shown to have the potent anti-tumor activity in human xenograft animal models and are being actively tested in clinical trials.

HIF-1 is a key regulator of many biological processes, including angiogenesis, energy metabolism, and cell survival (26,27). HIF-1 is composed of two subunits: the hypoxia-regulated α subunit, HIF-1α, and the oxygen-insensitive HIF-1ß subunit (28). Under normoxic conditions, the HIF-1α subunit is rapidly degraded via the ubiquitin-proteasome pathway triggered by oxygen-dependent hydroxylation of proline residues in HIF-1α (29,30). Under hypoxic conditions, this oxygen dependent-degradation system is repressed. HIF-1α is able to form a heterodimer with HIF-1ß, bind to hypoxia responsive elements (HREs) in oxygen-regulated genes and activate transcription (31,32).

In the present study, we confirmed that HDACIs significantly decrease HIF-1α protein level and transcriptional activity of HIF-1 in tumor cell lines. Moreover, HDAC1 and 3 directly interact with the ODD domain of HIF-1α, resulting in the increase of HIF-1α stability and HIF-1 transactivation function under hypoxia. Therefore, our results suggest that HDAC1 and 3 have the potential to upregulate HIF-1α stability in hypoxic conditions.

Materials and methods

Reagents and antibodies. Trichostatin A (TSA), sodium butyrate (SB), and valproic acid (VPA) were purchased from Sigma (St. Louis, MO), and apicidin from Calbiochem (Darmstadt, Germany).

Anti-HIF-1α antibodies were purchased from BD Pharmingen (San Diego, CA), Novus Biologicals (Littleton, CO), and Cayman Chemical (Ann Arbor, MI). Flag and GFP antibodies were purchased from Sigma and Santa Cruz Biotechnology (Santa Cruz, CA), respectively.

Plasmids. For luciferase assay, pBOS-hHIF-1α, pBOS-hHIF-1ß, and pSV40pro-EpoHRE-Luc vectors were kindly provided

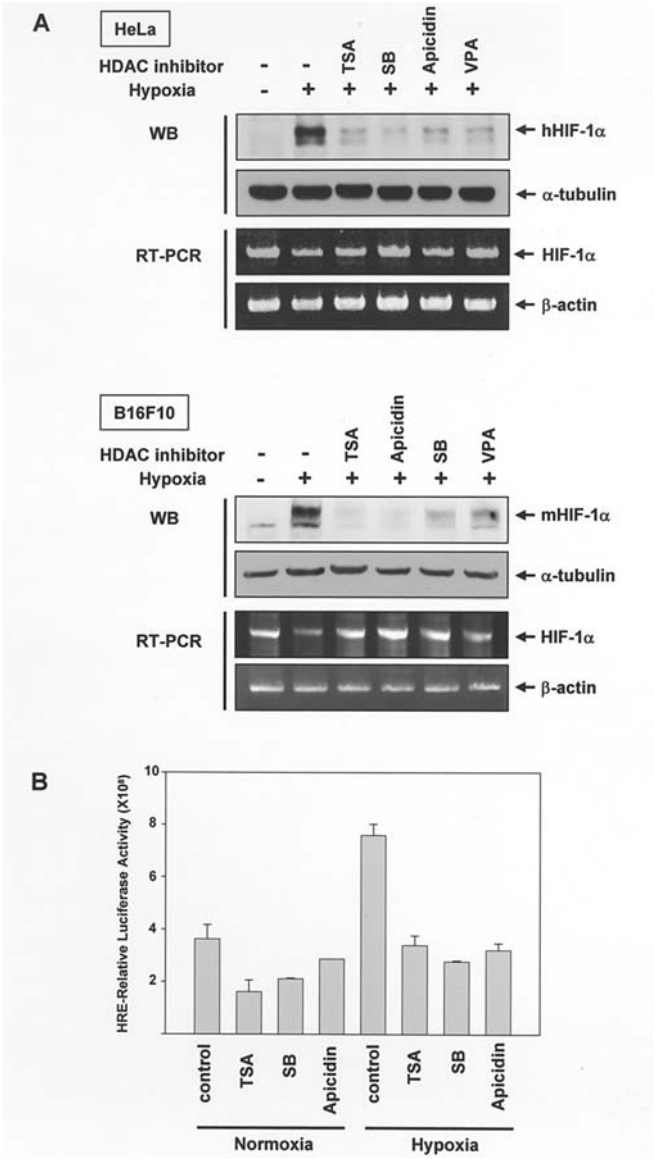

Figure 1. HDAC inhibitors downregulate HIF-1α stability and HIF-1 transcriptional activity. (A) HeLa or B16F10 cells under normoxia (21% O_2) or hypoxia (1% O_2) for 16 h with treatment of TSA (1 μM), sodium butyrate (SB) (2 mM), apicidin (1 μM), and valproic acid (VPA) (1 mM) were isolated. Protein extracts (30 μg) were examined by SDS-PAGE and analyzed by Western blotting with HIF-1α-specific antibody. α-tubulin served as a loading control. RT-PCR analysis was performed for HIF-1α and ß-actin with total RNA isolated from HeLa and B16F10 cells cultured under normoxia or hypoxia treated with TSA (1 μM), SB (2 mM), apicidin (1 μM), and VPA (1 mM) for 16 h. ß-actin served as a loading control. (B) 293T cells were cotransfected with pSV40pro-EpoHRE-Luc (1 μg), pBOS-hHIF-1α (0.1 μg), pBOS-hHIF-1ß (0.1 μg). Transfected cells were treated under normoxia or hypoxia with TSA (1 μM), SB (2 mM), and apicidin (1 μM) for 16 h. The mean and standard deviation based on three independent transfections are shown.

by Dr Y. Fujii-Kuriyama (Tohoku University, Japan) (33). Mammalian expression vectors, pcDNA3-HDAC1 and pcDNA3-HDAC3 were obtained from Dr W.M. Yang (National ChungHsing University, Taiwan). GFP-HIF-1α expression vector was prepared as previously described (34).

Cell culture and hypoxic condition. 293T, HeLa, and B16F10 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Gibco, Grant Island, NY) supplemented with 10% fetal bovine serum (FBS) (Gibco) and 1% antibiotics (Gibco). For hypoxic conditions, cells were incubated at a 5% CO_2 level with 1% O_2 balanced with N_2 in a hypoxic chamber (Forma Scientific, Marietta, OH).

Immunoprecipitation and Western blotting. Transfected cells were lysed in whole cell extract buffer (10 mM HEPES at pH 7.9, 400 mM NaCl, 0.1 mM EDTA, 5% glycerol, 1 mM DTT, protease inhibitors). Anti-Flag antibody (1μg) was added to the lysate, followed by Protein-A agarose (Upstate, Lake Placid, NY) in TEG reaction buffer (20 mM Tris-HCl at pH 7.4, 1 mM EDTA, 10% glycerol, 1 mM DTT, 150 mM NaCl), and the mixture was stirred overnight at 4˚C. The immunoprecipitates were washed in TEG washing buffer (TEG reaction buffer containing 0.1% Triton X-100), subjected to SDS-PAGE and transferred onto a nitrocellulose membrane (Amersham Pharmacia Biotech., Buckinghamshire, UK). The membrane was probed with primary antibodies followed by a secondary antibody conjugated with horseradish peroxidase and detected by the ECL plus system (Amersham Bioscience).

In vitro binding assay. Purified ODD protein and immunoprecipitated Flag-HDAC1/3 were mixed alone or together, and Flag-HDAC1/3 was immunoprecipitated with anti-Flag antibody in TEG reaction buffer. The immunoprecipitates were washed by TEG washing buffer three times and were subjected to SDS-PAGE and transferred onto nitro-cellulose membrane (Amersham Bioscience). Immunoblot analysis was carried out with anti-HIF-1α antibody.

Transient transfection and luciferase assays. Five micrograms of plasmids were transfected to 293T cells, with proper recombinations of effector plasmids using calcium phosphate-mediated methods (35). The luciferase and ß-galactosidase enzyme assays were performed as described (34). For overexpressing of HIF-1α or HDAC1/3 expression vectors, subconfluent 293T cells, in 60-mm or 100-mm dishes were transiently transfected with 5-10 μg empty, HIF-1α or HDAC1/3 plasmids using calcium phosphate-mediated methods. In HeLa and B16F10 cells, transient transfection was performed using Lipofectamine plus reagent (Invitrogen, Carlsbad, CA).

RT-PCR analysis. Total RNA was extracted using an RNA extraction kit (Invitrogen). Complementary DNA was synthesized from 4 μg total RNA using an oligo-dT primer. Primers used for PCR were hHIF-1α forward: 5' GGATCC TTAACTTTGCTGGCC 3' and reverse: 5' CCCGGGA GTCTGCTGGAATA 3'; mHIF-1α forward: 5' AGGTGAC TGTGCACCTA 3' and reverse: 5' GCTGTGAATGTG CTGTGA 3'; ß-actin forward: 5' GACTACCTCATGA AGATC 3' and reverse: 5' GATCCACATCTGCTGGAA 3'. Thirty cycles of PCR were carried out to amplify HIF-1α and ß-actin, and signals were detected by autoradiography.

Results

HDAC inhibitors downregulate HIF-1α stability and transcriptional activity of HIF-1. We tested the effect of

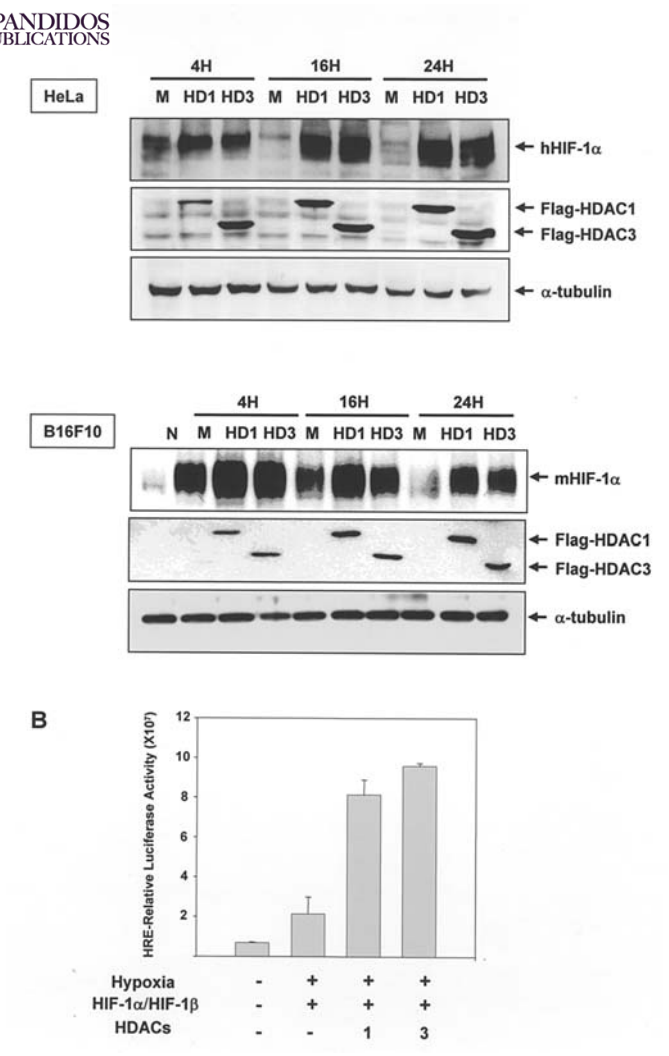

Figure 2. HDAC1 and 3 increase HIF-1α stability and transcriptional activity of HIF-1 under hypoxia. (A) HeLa or B16F10 cells were transfected with Flag-HDAC1/3 and incubated in hypoxia for 4, 16, or 24 h. Total cell extracts were analyzed by Western blotting with anti-HIF-1α, anti-Flag, and anti-α-tubulin antibodies, respectively. (B) 293T cells were cotransfected with pSV40pro-EpoHRE-Luc (1 μg), pBOS-hHIF-1α (0.1 μg), pBOS-hHIF-1ß (0.1 μg) and 2 μg of pcDNA-HDAC1 or pcDNA-HDAC3 or pcDNA alone. Transfected cells were incubated for 24 h at normoxia and then incubated at normoxia or hypoxia for an additional 16 h. The mean and standard deviation based on three independent transfections are shown.

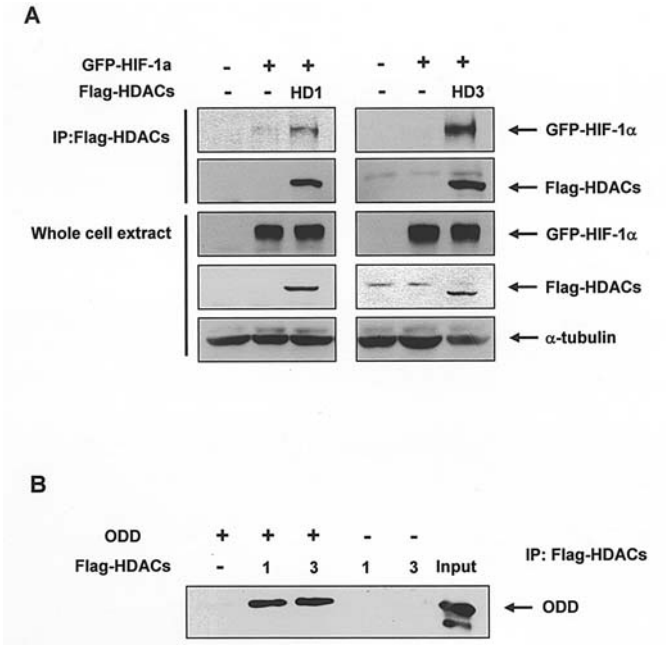

Figure 3. HDAC1 and 3 interact with HIF-1α *in vivo* and *in vitro*. (A) 293T cells were cotransfected with expression vectors for GFP-HIF-1α and/or pcDNA-Flag-HDAC1/3 or pcDNA alone. After transfection for 24 h, the cell extracts were prepared. Total cell lysates were immunoprecipitated with anti-Flag antibody. The presence of GFP-HIF-1α in the immunoprecipitants was examined using anti-GFP antibody. Immunoprecipitated materials and total cell extracts were analyzed by Western blotting with anti-Flag, anti-GFP, and anti-α-tubulin antibodies, respectively. (B) Immunoprecipitated Flag-HDAC1 and 3 were incubated in the absence or presence of recombinant ODD. After washing the mixture, the bound proteins were separated by SDS-PAGE and subjected to Western blot analysis for HIF-1α. IP, immunoprecipitation.

HDAC activity on HIF-1α expression in hypoxia-exposed cells using several HDACIs (TSA, SB, apicidin, and VPA). As shown in Fig. 1A, HDACIs dramatically decreased the amount of endogenous HIF-1α that was induced by hypoxia, while the inhibitory effect was not observed in the levels of HIF-1α mRNA transcripts in the human HeLa cervical cancer cell line. A similar result was obtained in the murine B16F10 melanoma cancer cell line. To further examine whether HDACIs affected the transactivation of HIF-1, we performed a luciferase reporter system, pSV40promoter-EpoHRE-Luc. Upon transient transfection of HIF-1α/HIF-1ß and EpoHRE-Luc vectors into 293T cells, the reporter activity was markedly inhibited by HDACIs under both normoxic and hypoxic conditions (Fig. 1B). These results suggested that HDACIs negatively regulate both HIF-1α protein level and HIF-1-mediated transcriptional activation. From the above results, we hypothesized that HDAC activity is closely associated with the stability of HIF-1α.

HDAC1 and 3 upregulate HIF-1α stability and transcriptional activity of HIF-1 in hypoxic conditions. A recent study reported that HDAC1 and HIF-1α were efficiently co-precipitated in human breast cancer cell line MCF-7, indicating that these proteins are capable of forming a complex *in vivo* under hypoxic conditions (36). From these observations, we tested whether class I HDACs, HDAC1 and 3 are involved in the regulation of HIF-1α protein in hypoxic conditions. Therefore, we transfected HDAC1/3 into HeLa or B16F10 cells and then exposed cells to hypoxia for 4, 16, or 24 h. As shown in Fig. 2A, overexpressed HDAC1 and 3 increased the endogenous HIF-1α protein level compared with hypoxia alone in both cell lines. In addition, to examine whether HDAC1 and 3 affected on HIF-1 transcriptional activity, we used a luciferase reporter system, pSV40promoter-EpoHRE-Luc reporter. Ectopic expression of HDAC1 and 3 enhanced the transcriptional activity of HIF-1 compared with hypoxia-stimulated activity in the absence of exogenous HDAC1 and 3 (Fig. 2B). Therefore, this finding indicated that HDAC1 and 3 have the potential to increase HIF-1α stability and HIF-1 transactivation function under hypoxia.

HDAC1 and 3 interact with HIF-1α in vivo and in vitro. To examine the association between HIF-1α and HDAC1/3, we

cotransfected 293T cells with GFP-HIF-1α and Flag-HDAC1/3. When Flag-HDAC1 and 3 proteins were immunoprecipitated from transfected cell extracts using the anti-Flag antibody, GFP-HIF-1α was coimmunoprecipitated (Fig. 3A). Since HDAC1 and 3 regulate the stability of HIF-1α (Fig. 2A), it is plausible that HDAC1 and 3 bind to the ODD domain of HIF-1α. To test this possibility, we performed *in vitro* binding assay using purified recombinant ODD protein and immunoprecipitated Flag-HDAC1 and 3. As shown in Fig. 3B, ODD protein was pulled down with HDAC1 or 3 (Fig. 3B). These results strongly suggested that HDAC1 and 3 directly associate with the ODD region of HIF-1α.

Discussion

HDACIs are considered to be anticancer drugs because of their potential to induce differentiation or apoptosis preferentially in cancer cells (37-39). Based on their persuasive proapoptotic and anti-angiogenic effects, deacetylase inhibitors are tested as potentially essential new chemotherapeutic agents for the remedy of solid tumors (40). Therefore, our results that HDACIs showed suppression of HIF-1α stability appear to play a key role in their anti-angiogenic effects (Fig. 1A) (41-43). In addition, the finding that HIF-1α expression is decreased by TSA suggests the involvement of class I and class II HDACs in the regulation of HIF-1α stability, because most class I/II HDACs are significantly inhibited by TSA, whereas class III HDACs are resistant to TSA. Here, we found that among class I HDACs, HDAC1 and 3 directly interacted with HIF-1α protein and then invoked HIF-1α stability and HIF-1 transactivation function under hypoxia. These results strongly indicate that the stabilization of HIF-1α protein is accelerated by interacting with HDAC1/3.

Recently, it was reported that N-terminal acetyltransferase, ARD1, interacts with the ODD domain of HIF-1α and then degrades HIF-1α through its acetylation (36,44,45). In addition, Yoo *et al* (36) reported that metastasis-associated protein 1 (MTA1) promotes the deacetylation of HIF-1α by increasing the expression of HDAC1. From previous studies, it seems likely that HDAC1 and 3 are involved in the regulation of HIF-1α stability via reversible acetylation. However, since pVHL functions as a corepressor by recruiting HDAC1/3 to HIF-1α (46), further investigations would be necessary to elucidate the regulatory mechanism of HIF-1α stability by multi-protein complexes consisting of HDAC1/3 and pVHL.

Through an evaluation of the collective evidence, we conclude that HDACIs have an inhibitory effect on HIF-1α stability and HIF-1 transactivation function in human and mouse tumor cell lines. Furthermore, HDAC1 and 3 associate with the ODD domain of HIF-1α and then potentiate the transcriptional activity of HIF-1 by stabilizing HIF-1α protein. Taken together, these results are important in understanding the mechanism for HDACIs' anti-angiogenic and anti-tumorigenic activities.

Acknowledgements

We thank Dr Y. Fujii-Kuriyama for the gifts of pBOS-hHIF-1α, pBOS-hHIF-1ß, and pSV40pro-EpoHRE-Luc vectors. We also thank Dr W.M. Yang (National ChungHsing University, Taiwan) for providing pcDNA3-HDAC1 and pcDNA3-HDAC3 expression vectors. This work was supported by the Creative Research Initiatives (NeuroVascular Coordination Research Center) of MOST/KOSEF, Korea.

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