HDAC1 promotes the migration of human myeloma cells via regulation of the lncRNA/Slug axis

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Abstract. Understanding the mechanisms underlying malignancy in myeloma cells is important for targeted treatment and drug development. Histone deacetylases (HDACs) can regulate the progression of various cancer types; however, their roles in myeloma are not well known. In the present study, the expression of class I HDACs in myeloma cells and tissues was evaluated. Furthermore, the effects of HDAC1 on the migration of myeloma cells and the associated mechanisms were investigated. Among the class I HDACs evaluated, HDAC1 was upregulated in both myeloma cells and tissues. Targeted inhibition of HDAC1 suppressed the migration of myeloma cells. Of the assessed transcription factors, small interfering (si)-HDAC1 decreased the expression of Slug. Overexpression of Slug reversed the si-HDAC1-mediated suppressed migration of myeloma cells. Mechanistically, the results revealed that HDAC1 regulated the mRNA stability of Slug, while it had no effect on its transcription or nuclear export. Furthermore, HDAC1 negatively regulated the expression of long non-coding RNA (lncRNA) NONHSAT113026, which could bind with the 3'-untranslated region of Slug mRNA to facilitate its degradation. The present study demonstrated that HDAC1 promoted the migration of human myeloma cells via regulation of lncRNA/Slug signaling.

Introduction

Multiple myeloma (MM) is a hematological malignancy that is characterized by the abnormal expansion of monoclonal plasma cells in the bone marrow (1). MM is the most common hematological cancer worldwide, and it accounts for ~13% of all hematological malignancies (2). Various therapy approaches, including chemotherapy, autologous/allogeneic stem cell transplantation and monoclonal antibodies, have been developed for MM treatment (3,4). However, the clinical therapeutic efficiency of MM remains unsatisfactory (5-7). E-cadherin (E-Cad) protein, an inhibitor of epithelial-mesenchymal transition (EMT), was reported to be decreased in metastatic MM tissues, while the expression of Slug, MMP-2 and MMP-9 proteins was increased (8). Therefore, research on the mechanisms underlying MM development and cell migration are required to improve patient outcomes.

Genetic and epigenetic abnormalities, such as chromosomal translocations and histone acetylation, are common features of MM (9-12). Histone deacetylases (HDACs) can remove acetyl groups from N-acetyllysines on histones to regulate the progression of various cancer types, including MM (13). Targeted inhibition of HDAC can induce cell cycle arrest and apoptosis of cancer cells (14). Inhibitors of HDAC, such as butyrate, trichostatin A and suberoylanilide hydroxamic acid, have been considered as candidate drugs for cancer therapy (15,16). Peptides that inhibit HDAC can overcome bortezomib resistance in MM (18). Nexturastat A, the selective inhibitor of HDAC6, can induce apoptosis, overcome drug resistance and inhibit tumor growth in MM (19). Overall, these data suggest that HDACs may play important oncogenic roles in MM development.

Aberrant overexpression of class I HDACs (HDAC1, 2, 3 and 8) has been observed in MM tissues (20). In addition, class-I HDACs may serve more important roles in cancer progression than other HDACs, among the 18 HDAC enzymes identified in humans (21,22). However, to the best of our knowledge, no attempt has been made thus far to explain the roles and underlying mechanisms of class I HDACs in MM development.

The aim of the present study was to investigate whether HDAC1 can positively regulate the migration of MM cells, and to perform mechanistic studies in order to determine whether HDAC1 promotes the malignancy of human MM cells via regulation of long non-coding RNA (lncRNA) NONHSAT113026/Slug signaling.

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Materials and methods

Cell lines and cell culture. Human MM U266, RPMI8226 and H929 cells were purchased from The Cell Bank of Type Culture Collection of The Chinese Academy of Sciences. The human normal plasma cell line (nPCs) was acquired from BeNa Culture Collection (cat. no. BNCC350752; http://www.bncc.org.cn/pro/pl/5/p_943.html). All cells were cultured in RPMI-1640 medium (HyClone; Cytiva) supplemented with 10% FBS (FBS; cat. no. S601P-500; Sera Pro), 1% L-glutamine and 1% penicillin/streptomycin in humidified air with 5% CO₂ at 37°C.

RNA extraction and reverse transcription-quantitative PCR (RT-qPCR). Total RNA from human MM cells was extracted using TRIzol® (Thermo Fisher Scientific, Inc.) following the manufacturer's instructions. After isolation, 500 ng total RNA was used to generate complementary DNA using PrimeScript RT Reagent kit (Takara Biotechnology Co., Ltd.) at room temperature according to the manufacturer's protocol. qPCR was performed using SYBR Green PCR kit (Applied Biosystems; Thermo Fisher Scientific, Inc.) and analyzed with MyiQ Real Time RT-PCR System (Bio-Rad Laboratories, Inc.) at 95°C, followed by 40 cycles for 10 sec at 95°C, 30 sec at 60°C and 1 sec at 72°C, and 1 cycle of cooling for 30 sec at 50°C.

The primer sequences used in the present study were as follows: HDAC1 forward, 5'-CTACTACGACGGGATGTGAGG-3' and reverse 5'-GAGTCTAGCCGATTGCTGAG-3'; HDAC2 forward, 5'-ATGGGCTCAGCTCAAGGAGG-3' and reverse, 5'-TGGGATCTTCTATGGGCTTCCA-3'; HDAC3 forward, 5'-CCTGGCAATCAGCCATGCC-3' and reverse 5'-CTTCTGTTGAGGCTGGCATA-3'; HDAC8 forward, 5'-TCGCTGTCGCCCTTATATAC-3' and reverse, 5'-TACCCGGGCGTTTTG-3'; MMP-2 forward, 5'-ATCAGCAGTGGACGGCAGG-3' and reverse, 5'-AGATGACCGTTCGACGG-3'; NONHSAT113026 forward, 5'-GACUAACAGAAGGA-3' and reverse, 5'-AGATGACCGTTCGACGG-3'; and HDAC1 forward, 5'-CATTACGACGGGATGTGAGG-3' and reverse 5'-GAGTCTAGCCGATTGCTGAG-3'.

 Luciferase assays. The luciferase reporter construct pGL-Slug was generated by inserting the promoter of Slug (-1,000 to +1 bp) according to a previous study (24). The dual-luciferase reporter construct pGL-Slug was used to normalize the loading control for normalization. The signals were detected by enhanced chemiluminescence using a Chemidoc XRS Molecular Imager (Bio-Rad Laboratories Inc.). Quantity One software (version 4.3.0; Bio-Rad Laboratories, Inc.) was used for densitometric analysis.

Cell transfection. Cells were seeded in 6-well plates at 50-60% confluence. Cell transfection was conducted using Lipofectamine® 3000 reagent (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions at room temperature. The time interval between transfection and subsequent experimentation was 24 h.

For overexpression, the sequence of Slug was cloned into the pcDNA vector (Invitrogen; Thermo Fisher Scientific, Inc.) to construct the overexpression vector pcDNA-Slug, and empty pcDNA was used as the NC. Cells seeded in 6-well plates at ~60% confluence were transfected with vector control, plasmid constructs (final concentration of 20 µg/ml) or siRNAs (final concentration of 20 nmol/l). The transfection efficiency was evaluated by western blot analysis and/or RT-PCR.

Wound healing assay. Cells were transiently transfected with siRNA or plasmid as aforementioned. Straight lines were drawn vertically on the back of a 12-well plate before seeding the cells. When the cells reached 90% confluence, the cell monolayer was gently scratched with a 100-µl pipette tip according to the marked lines and washed with PBS three times. Next, RPMI-1640 medium (HyClone; Cytiva) without FBS was added to the plate. The imaging position was recorded at 0 and 24 h by using an inverted microscope (Leica Microsystems GmbH; magnification, x10). The results were determined by calculating the area occupied by migrated cells at five random areas for each wound as follows: (Original wound width at 0 h-actual wound width at 24 h)/(original wound width at 0 h).

Western blot analysis. Cells were lysed using RIPA buffer (Santa Cruz Biotechnology, Inc.) supplemented with a protease inhibitor cocktail (Roche Applied Science). Protein concentration was determined using a NanoDrop ND-1000 UV-Vis Spectrophotometer (NanoDrop Technologies; Thermo Fisher Scientific, Inc.). Next, 30 µg total protein from each lysate was separated using 10 or 12% SDS-PAGE and subsequently electroblotted onto a PVDF membrane. The membranes were blocked with 5% skimmed milk at room temperature for 2 h. The target proteins were probed with primary antibodies (1:1,000) overnight at 4°C and further incubated with HRP-conjugated secondary antibody (cat. no. ab7090; Abcam; 1:10,000). The primary antibodies were specific for GAPDH (cat. no. ab181602; Abcam), HDAC1 (cat. no. ab53091; Abcam), HDAC2 (cat. no. ab7029; Abcam), HDAC3 (cat. no. ab96005; Abcam), HDAC8 (cat. no. 17548-1-AP; ProteinTech Group, Inc.), MMP-2 (cat. no. ab97779; Abcam), MMP-9 (cat. no. PA5-27191; Thermo Fisher Scientific, Inc.), E-cad (cat. no. ab231303; Abcam) and Slug (cat. no. ab27568; Abcam). GAPDH was used as the loading control for normalization. The signals were detected by enhanced chemiluminescence using a Chemidoc XRS Molecular Imager (Bio-Rad Laboratories Inc.). Quantity One software (version 4.3.0; Bio-Rad Laboratories, Inc.) was used for densitometric analysis.
expression plasmids pGL-Slug and pGL3-IE1-Rluc (50 ng, Promega Corporation) were co-transfected into cells. After ~24 h, luciferase activity was determined with Dual-Glo Luciferase Assay kit (Promega Corporation) according to the manufacturer's instructions by using a multilabel plate reader (Wallac VICTOR; PerkinElmer, Inc.). The relative luciferase activity (firefly luciferase/Renilla luciferase) was calculated. Each experiment was repeated three times.

Cell nuclear and cytoplasmic RNA isolation. Nuclear and cytoplasmic RNA were extracted from U266 cells using the PARIS kit (Thermo Fisher Scientific, Inc.) and TRIzol® (Thermo Fisher Scientific, Inc.), according to a previous study (25).

mRNA stability assay. Cells were pre-transfected with si-NC or si-HDAC1 for 24 h and then further treated with 5 µg/ml actinomycin D (Act-D; cat. no. A9415; Sigma-Aldrich; Merck KGaA) for 0 to 8 h. Total RNA was extracted by using TRIzol®, and the levels of Slug were analyzed by using RT-qPCR, as aforementioned. The levels of Slug were normalized to those of GAPDH.

Oncomine database analysis. The online microarray database Oncomine™ was used to explore the mRNA expression levels of HDAC1 in MM and adjacent normal tissues (https://www.oncomine.org/resource/login.html). The conditions for filter settings were as follows: Gene, ‘HDAC1’; Cancer Type, ‘Myeloma’.

Statistical analysis. Data are presented as the mean ± standard deviation from ≥3 separate experiments. Statistical differences were determined by performing an unpaired two-tailed Student's t-tests and one-way ANOVA followed by Bonferroni’s post hoc test using SPSS 15.0 (SPSS, Inc.). GraphPad Prism 8.0 software (GraphPad Software, Inc.) was used to represent data on graphs. P<0.05 was considered to indicate a statistically significant difference.

Results

**HDAC1 is increased in MM cells and tissues.** Firstly, the mRNA and protein levels of class I HDACs in MM U266, RPMI8226 and NCI-H929 cells, and in nPcs cells were determined. RT-qPCR revealed that the expression of HDAC1, but not of HDA2, -3 or -8, was significantly upregulated in MM cells compared with that in nPcs cells (Fig. 1A). Furthermore, western blot analysis also confirmed the upregulation of HDAC1 in MM cells (Fig. 1B).

The present study also evaluated the expression of HDAC1 in MM and normal tissues with data from the Oncomine database. The results revealed a significantly increased expression of HDAC1 in MM tissues compared with that in adjacent normal tissues according to the data reported by Talantov (Fig. 1C) and Haqq (Fig. 1D) on myeloma. Overall, these data indicated that HDAC1 was upregulated in MM cells and tissues.

**HDAC1 regulates the migration of MM cells.** In order to evaluate the potential roles of HDAC1 in the progression of MM, human MM U266 and RPMI8226 cells were transfected with HDAC1 siRNA (Fig. 2A). The data showed that si-HDAC1 could significantly decrease the migration of U266 and RPMI8226 cells, compared with the si-NC (Fig. 2B). RT-qPCR revealed that si-HDAC1 treatment decreased the mRNA expression of MMP-2 and MMP-9, as well as increasing the expression of E-Cad, in U266 (Fig. 2C) and RPMI8226 (Fig. 2D) cells.

Western blot analysis confirmed that si-HDAC1 decreased the expression of MMP-2 and MMP-9, and increase the expression of E-Cad, in U266 cells (Fig. 2E), which indicated that HDAC1 regulated the migration of MM cells.

**Slug is essential for the HDAC1-regulated motility of MM cells.** Transcription factors such as Snail, Slug, Zeb1 and Twist, which can trigger the EMT of cancer cells, are critical for the motility of cancer cells (26,27).

The present study found that si-HDAC1 significantly decreased the mRNA expression level of Slug, but not that of Snail, Zeb1 or Twist, in U266 (Fig. 3A) and RPMI8226 (Fig. 3B) cells. Western blot analysis confirmed that si-HDAC1 decreased the protein expression of Slug in U266 and RPMI8226 cells (Fig. 3C).

The effects of Slug on the si-HDAC1-suppressed migration of U266 cells were evaluated via overexpression of Slug (Fig. 3D). Migration assay showed that overexpression of Slug could reverse the si-HDAC1-suppressed migration of U266 cells (Fig. 3E). In addition, overexpression of Slug also attenuated the si-HDAC1-increased expression of E-Cad in U266 cells (Fig. 3F). These data revealed that Slug was essential for the HDAC1-mediated regulation of motility of MM cells.

**HDAC1 positively regulates the mRNA stability of Slug.** The mechanism underlying the HDAC1-regulated expression of Slug was next investigated. The present data indicated that si-HDAC1 had no effect on the precursor mRNA expression of Slug in either U266 or RPMI8226 cells (Fig. 4A).

Furthermore, the promoter of Slug (-1,000 to +1) was subcloned in the pGL3 luciferase reporter. Dual-luciferase assay showed that si-HDAC1 had no effect on the promoter activity of Slug in MM cells (Fig. 4B).

By separating nuclear and cytoplasmic RNA, RT-qPCR analysis showed that si-HDAC1 had no effect on the nuclear export of Slug in MM cells (Fig. 4C). However, si-HDAC1 could significantly decrease the mRNA stability of Slug in both U266 (Fig. 4D) and RPMI8226 (Fig. 4E) cells. These results indicated that HDAC1 could positively regulate the mRNA stability of Slug.

**HDAC1 negatively regulates the expression of lncRNA-NONHSAT113026 in MM cells.** It has been reported that lncRNA can bind to mature mRNA to regulate mRNA stability in cancer cells (28,29). lncRNA NONHSAT113026 can bind the 3'-untranslated region (UTR) of Slug via direct lncRNA-mRNA interactions, which results in the degradation of mRNA (30). The present results showed that knockdown of HDAC1 significantly increased the expression of lncRNA NONHSAT113026 in U266 and RPMI8226 cells (Fig. 5A).

Furthermore, knockdown of lncRNA NONHSAT113026 was successfully performed (Fig. 5B) and this resulted in increased migration of U266 cells (Fig. 5C). In addition, knockdown of lncRNA NONHSAT113026 could increase...
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Figure 1. HDAC1 is increased in MM cells and tissues. (A) The mRNA expression of class I HDACs in MM and nPCs cells were evaluated. (B) The protein expression of HDACs in MM and nPCs cells were determined. Expression of HDAC1 in human MM cancer tissues and normal mucosa tissues from (C) Talantov and (D) Haqq myeloma datasets from the Oncomine database. Data are presented as mean ± SD of three independent experiments. *P<0.01. HDAC1, histone deacetylase 1; MM, multiple myeloma; nPCs, normal plasma cells.

Figure 2. HDAC8 regulates the migration of MM cells. (A) Cells were transfected with si-NC or si-HDAC1-1 or -2 for 24 h, the protein expression of HDAC1 was checked; si-HDAC1-1 was used for subsequent experiments. (B) Wound healing assay for cells transfected with si-NC or si-HDAC1 for 24 h. (C) U266 and (D) RPMI8226 cells were transfected with si-NC or si-HDAC1 for 24 h, the mRNA expression of MMP2, MMP9 and E-Cad was evaluated. (E) U266 cells were transfected with si-NC or si-HDAC1 for 24 h, the protein expression of MMP2, MMP9 and E-Cad was determined and quantitatively analyzed. Data are presented as the mean ± SD of three independent experiments. *P<0.01. HDAC1, histone deacetylase 1; MM, multiple myeloma; si, small interfering; NC, negative control; E-Cad, E-Cadherin.
Figure 3. Slug is essential for HDAC1-regulated motility of MM cells. (A) U266 and (B) RPMI8226 cells were transfected with si-NC or si-HDAC1 for 24 h, the mRNA expression was determined via RT-qPCR. (C) Cells were transfected with si-NC or si-HDAC1 for 24 h, the protein expression of Slug was checked. (D) U266 cells were co-transfected with si-NC, si-HDAC1, vector control or pcdNA/Slug for 24 h. (E) Expression of Slug was determined by western blot analysis. (F) Migration was assessed by wound healing assay. (G) The expression of E-Cad was checked by western blot analysis. Data are presented as the mean ± SD of three independent experiments. **P<0.01, NS, not significant; HDAC1, histone deactylase 1; MM, multiple myeloma; si, small interfering; NC, negative control; Vec, vector.

Figure 4. HDAC1 positively regulates the mRNA stability of Slug. (A) Cells were transfected with si-NC or si-HDAC1 for 24 h, the precursor mRNA of Slug was determined by RTq-PCR. (B) Cells were co-transfected with si-NC, si-HDAC1 or pGL3-Slug for 24 h, the promoter activity was evaluated via dual-luciferase assay. (C) Total RNA from the cytoplasm and nucleic fraction of U266 cells transfected with si-NC or si-HDAC1 for 24 h were isolated, the levels of Slug mRNA was measured. (D) U266 or (E) RPMI8226 cells were pre-transfected with si-NC or si-HDAC1 for 24 h and then further treated with Act-D for the indicated time periods before the mRNA expression of Slug was measured. Data are presented as the mean ± SD of three independent experiments. **P<0.01. HDAC1, histone deactylase 1; MM, multiple myeloma; si, small interfering; NC, negative control; Cyto, cytoplasm; Nucl, nucleus; Con, control.
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The expression of MMP-2 and MMP-9, and decrease the expression of E-Cad, in both U266 (Fig. 5D) and RPMI8226 (Fig. 5E) cells. These results suggested that HDAC1 negatively regulated the expression of lncRNA-NONHSAT113026 in MM cells.

**Figure 5.** HDAC1 negatively regulates the expression of lncRNA NONHSAT113026 in MM cells. (A) Cells were transfected with si-NC or si-HDAC1 for 24 h, the expression of lncRNA NONHSAT113026 was measured via RT-qPCR. (B) Cells were transfected with si-NC or si-lncRNA NONHSAT113026 for 24 h, the expression of lncRNA NONHSAT113026 was measured. (C) U266 cells were transfected with si-NC or si-lncRNA NONHSAT113026 for 24 h, cell migration was evaluated by wound healing assay. (D) U266 or (E) RPMI8226 cells were pre-transfected with si-NC or si-lncRNA NONHSAT113026 for 24 h and then expression of MMP2, MMP9 and E-Cad were measured via RT-qPCR. Data are presented as the mean ± SD of three independent experiments. *P<0.01. HDAC1, histone deacetylase 1; MM, multiple myeloma; si, small interfering; NC, negative control; lnc, long non-coding; E-Cad, E-cadherin.
suppress the expression of Slug, while overexpression of Slug can rescue si-HDAC1-inhibited cell migration. These findings confirmed the essential roles of Slug in the HDAC1-regulated progression of MM.

lncRNA NONHSAT113026-regulated mRNA stability is involved in the HDAC1-regulated expression of Slug. The present data showed that HDAC1 can regulate the mRNA stability of Slug, while it had no effect on its transcription or nuclear export. NONHSAT113026, which is localized at 6p12.3 and has a 7,682-bp RNA sequence encompassing four exons, was reported to be increased in renal cell carcinoma compared with matched non-tumor tissues (42). It can directly bind to the 3'-UTR of Slug mRNA to trigger mRNA degradation via direct lncRNA-mRNA interactions that arise from hybridization of homologous sequences (30). Knockdown of HDAC1 can significantly increase the expression of NONHSAT113026; however, the detailed mechanisms need further investigation. In addition, a previous study also indicated that HDAC1 can recruit and antagonize Slug E-box binding (43); however, whether this also occurs in MM cells needs further research.

In conclusion, the present study demonstrated that HDAC1 was upregulated in MM cells and tissues, and targeted inhibition of HDAC1 suppressed the migration of MM cells via downregulation of Slug. Mechanistic studies indicated that si-HDAC1 can decrease mRNA stability via upregulation of lncRNA-NONHSAT113026. It should be noted that the expression of HDAC1 was increased in cultured cell lines. Future studies should continue to isolate and culture patients' primary...
MM cells to validate the present conclusion. The current findings indicated that targeted inhibition of the HDAC1/Slug axis may represent a potential therapeutic option for patients with MM.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Authors’ contributions

LZ, JL, ML, MH and YZ conceived and designed the study. LZ, JL and AZ acquired the data. ML and YZ analyzed and interpreted the data. LZ and JL wrote and revised the manuscript. The authenticity of the raw data has been assessed by all authors. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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