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RESEARCH PAPER

HDAC11 promotes meiotic apparatus assembly during mouse oocyte maturation via decreasing H4K16 and α-tubulin acetylation

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ABSTRACT

The smallest histone deacetylase (HDAC) and the solely member of class IV, HDAC11, is reported to regulate mitosis process and tumorigenesis, yet its roles in meiosis process remain unknown. In the present study, we first analyzed the expression of HDAC11 in mouse oocytes. HDAC11 showed gradual lower expression from GV (Germinal Vesicle) to MII (Metaphase II) stage oocytes. Then, the specific inhibitor of HDAC11, JB3-22 was used to explore the role of HDAC11 during mouse oocytes maturation. We found that inhibition of HDAC11 significantly interrupted mouse oocytes meiosis progress, caused abnormal spindle organization and misaligned chromosomes, impaired kinetochore-microtubule attachment and spindle assembly checkpoint (SAC) function. Moreover, HDAC11 inhibition significantly increased the acetylation level of α-tubulin that is associated with microtubule stability, and increased acetylation level of H4K16 that is important for kinetochore function. In conclusion, our study indicates that HDAC11 is an essential factor for oocytes maturation and it promotes meiotic process most likely though decreasing acetylation status of α-tubulin and H4K16.

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Introduction

Unlike mitosis, meiosis consists of two consecutive rounds of chromosome separation with a single round of DNA replication. Chromosome segregation errors in oocyte meiosis could lead to aneuploidy, which is a leading cause of spontaneous abortions, birth defects and congenital defects in humans [1–3]. Chromosome segregation is driven by the spindle microtubules. The attachment between microtubules and kinetochores provides the major force that drives chromosome segregation [4]. While spindle assembly checkpoint (SAC) plays strict surveillance on anaphase onset until the stable kinetochore-microtubule attachment is formed, thus ensuring equal division of chromosomes into daughter cells [5]. Many regulators that plays cell cycle arrestment roles in mitosis are expected to play similar roles in meiosis. However, only a few of them have been confirmed [6,7].

Histone deacetylases (HDACs) regulate many biological functions by removing acetyl groups from lysine ε-amino group on proteins [8]. Till now, 18 isoforms of mammalian HDACs have been identified and they are generally classified into four groups: class I (HDACs 1, 2, 3 and 8), class II (HDACs 4,5, 6, 7, 9 and 10), class III (SIRTs 1–7) and class IV (HDAC11) [9,10]. Recently, several HDAC members were indicated to participate in the oocytes maturation process. For instance, conditionally deleting HDAC1 and HDAC2 would cause infertility in female mouse [11]. Specifically, targeting maternal HDAC2 impaired kinetochore function via decreasing H4K16 acetylation in mouse oocytes [12]. HDAC3 and HDAC6 regulated chromosome alignment and spindle assembly by modulating the acetylation status of α-tubulin [13–15]. HDAC11 is the smallest HDAC and it is the sole member of HDAC IV family, sharing sequence similarity to both class I and II HDAC proteins [16]. HDAC11 primarily localizes to the nucleus and is normally found in the brain, testis and immune cells [17,18]. Few studies on HDAC11 focused on its role in immune cells [18,19]. Recently, a study demonstrated that HDAC11 was required for mitotic cell cycle progression and survival in neuroblastoma cell lines [20]. However, the functions of HDAC11 in meiosis remain unknown.

Elevenostat (JB3-22) is a small molecule hydroxamic acid derivative that acts as a HDAC11-selective

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inhibitor [21]. In the present study, by using JB3-22, we investigated the potential roles of HDAC11 on mouse oocyte maturation and meiotic apparatus. We also detect the acetylation level of H4K16 and α-tubulin after HDAC11 inhibition. Our study provide insights into the meiosis modulatory functions of HDAC11 and suggest potential pathways how it modulate meiotic apparatus assembly.

Results

HDAC11 inhibition influences mouse oocyte maturation process

We firstly analyzed the dynamic mRNA expression of *HDAC11* in different stages of *in vitro* maturated oocytes. *HDAC11* showed similar expression in GVBD and GV oocytes, *HDAC11* expression in MI and MII stage were significantly lower ($P < 0.01$) than GV oocytes (Figure 1(a)).

We next examined the effect of HDAC11 on mouse oocytes GVBD and maturation using its inhibitor, JB3-22 (5 μM and 10 μM). After 4 h culture, 5 μM JB3-22 treated oocytes resumed meiosis normally compared with control oocytes, as evidenced by the similar GVBD rate (Figure 1(b)). However, 10 μM treatment group showed a significantly lower ($P < 0.01$) GVBD rate (43.3 ± 0.9) than that of the control oocytes (66.4 ± 3.0) (Figure 1(b)). After 16 h culture, Most control and 5 μM JB3-22 treated oocytes extruded the polar body and developed to the MII stage (Figure 1(d)), whereas treatment with 10μM JB3-22 resulted in the failure of polar body extrusion (Figure 1(d)), with 10μM treatment group showed significantly lower ($P < 0.01$) maturation rates (39.7 ± 2.8) than the control oocytes (69.6 ± 1.8) (Figure 1(c,d)). To identify the underlying mechanism that HDAC11 inhibition disturbing mouse oocytes maturation, 10 μM JB3-22 treated oocytes were subjected to further study.

HDAC11 inhibition caused aberrant spindle organization and misaligned chromosome during oocytes maturation

The effects of HDAC11 inhibition on maturation progression prompted us to investigate whether HDAC11 inhibition influenced the meiotic apparatus in oocytes. After 7 h *in vitro* culture, control and JB3-22 treated oocytes matured to MI stage. These oocytes were immunolabeled with an anti-tubulin antibody to visualize the spindle and

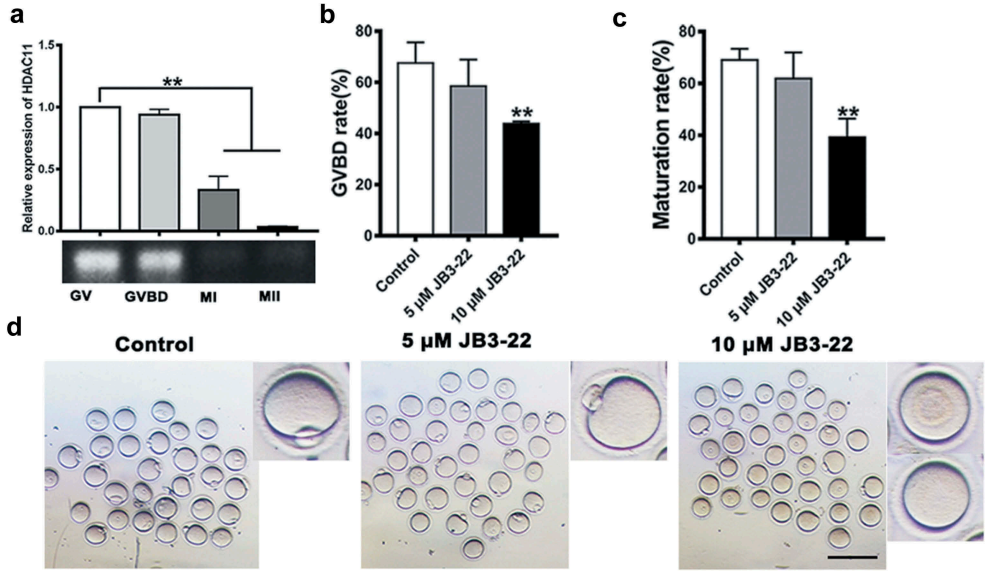

Figure 1. Expression of *HDAC11* in oocytes and effects of HDAC11 inhibition on mouse oocyte maturation.

(a) The qPCR and gel electrophoresis analysis of HDAC11 expression in GV, GVBD, MI and MII oocytes. Expression of HDAC11 in GV oocytes was used as a normalizer. The expression level of HDAC11 in GV oocytes was used as a calibrator (expression set to 1). (b) Quantitative analysis of GVBD rate in control, 5 μM and 10 μM JB3-22 treated oocytes. (c) Quantitative analysis of maturation rate in control, 5 μM and 10 μM JB3-22 treated oocytes. ☒d☒Images of control and JB3-22-treated (5 μM and 10 μM) oocytes. Scale bar, 200 μm. The graph shows the mean ± SE of the results obtained in three independent experiments. *$P < 0.05$, **$P < 0.01$ vs Control.

counterstained with Hoechst to observe chromosome alignment. As expected, control oocytes at MI stage usually showed a typical barrel-shape spindle with the well-aligned chromosomes, while JB3-22 treatment caused spindle disorganization and chromosome misalignment (Figure 2(a)). Compared with the control group (20.2 ± 1.1), the percentage of oocytes with misaligned chromosomes was significantly higher in JB3-22 treatment group (60.0 ± 2.0, $P < 0.01$) (Figure 2(b)). The percentage of oocytes with abnormal spindles was significantly higher in JB3-22 treatment group (56.5 ± 3.5, $P < 0.01$) than in the control group (16.7 ± 3.4) (Figure 2(a, b)).

HDAC11 inhibition caused K-MT mis-attachment

Accurate chromosome alignment and segregation depend on the proper attachment of kinetochores to microtubules emanating from opposite spindle poles [22]. The high percentage of spindle/chromosome abnormalities in HDAC11 inhibited oocytes may predict the compromised K-MT attachment. To test this, MI oocytes were labeled with CREST antibody to detect kinetochores, with anti-tubulin antibody to visualize spindle, and co-stained with Hoechst 33342 for chromosomes (Figure 3(a)). By confocal scanning, we observed an obvious increased K-M mis-attachment in JB3-22 treatment group (55.7 ± 2.4, $P < 0.01$) relative to control oocytes (18.6 ± 1.4) (Figure 3(b)).

HDAC11 inhibition impaired SAC function

A higher rate of meiotic arrest and impaired K-MT attachment in JB3-22 treated oocytes suggests that SAC might be activated. To gain insight into this issue, control and JB3-22 treated oocytes were immunolabeled for BubR1, an integral part of SAC, to indicate the SAC activation. BubR1 was localized to the unattached kinetochores at prometaphase I stage in control oocytes. However, BubR1 was lost from most of kinetochores in JB3-22 treated oocytes, indicating that HDAC11 inhibition impairs the SAC complex (Figure 4(a)).

Low concentration of Nocodazole (NOCO) (50 ng/ml) is safe to maintain intact spindle structure but strong enough to disrupt the connection between spindle microtubules and chromosome kinetochores, then recruiting SAC proteins to block anaphase onset [23]. To further testify if the function of SAC is impaired after HDAC11 inhibition, GV oocytes were

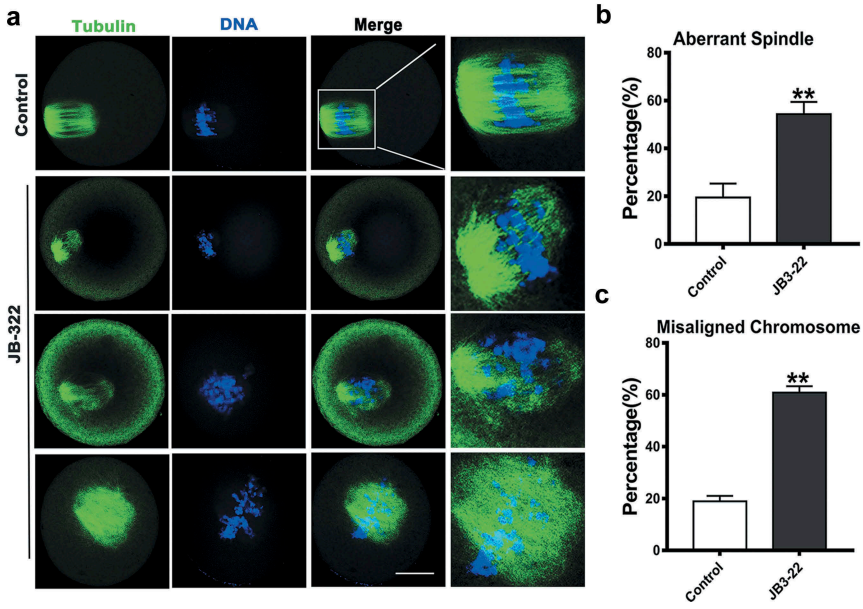

Figure 2. JB3-22 treatment caused spindle/chromosome abnormalities in mouse oocytes.

(a) Images of spindle morphologies and chromosome alignment in control and JB3-22-treated oocytes. Scale bar, 20 μm. (b) The proportion of abnormal spindles was recorded in control and JB3-22-treated oocytes. (c) The proportion of misaligned chromosomes was recorded in control and JB3-22 treated oocytes. Data were presented as mean percentage (mean ± SE) of at least three independent experiments. *$P < 0.05$, **$P < 0.01$.

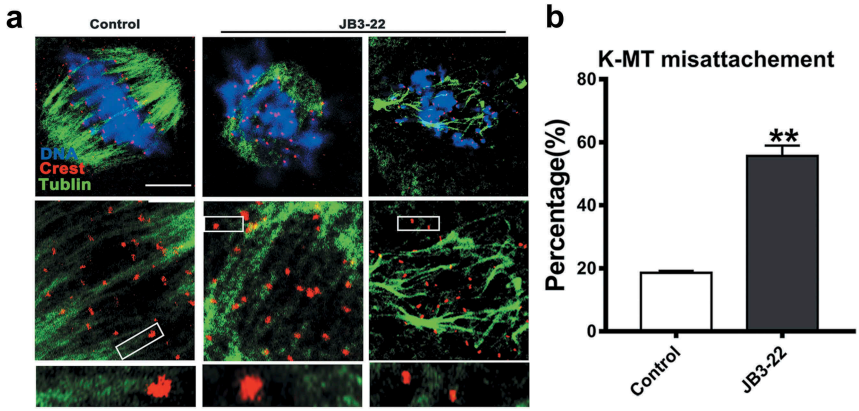

Figure 3. JB3-22 treatment caused defective K-M attachment in mouse oocytes.

(a) Images of kinetochore–microtubule attachment in control and JB3-22-treated oocytes. MI oocytes were labeled with CREST antibody for kinetochores (red), anti-tubulin antibody for microtubules (green) and Hoechst 33,342 for chromosomes (blue). Scale bar, 5 μm. **(b)** The rate of defective kinetochore–microtubule attachment was recorded in control and JB3-22 treated oocytes. Data were presented as mean percentage (mean ± SE) of at least three independent experiments. *$P < 0.05$, **$P < 0.01$.

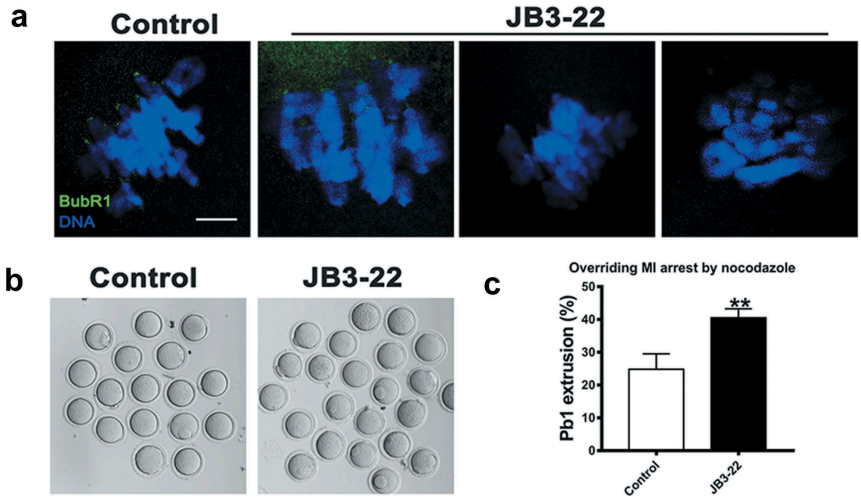

Figure 4. JB3-22 treatment impairs SAC during oocytes meiosis.

(a) Control and JB3-22 treated oocytes were immune-stained with anti-BubR1 antibody (green) and counterstained with Hoechst to examine chromosome (blue). Confocal images of pre-metaphase I and metaphase I oocytes are shown. Scale bar, 25 μm. (b) Images of first polar body extrusion (PBE) in control and JB3-22 treated oocytes treated with 50 ng/mL nocodazole at the time point of 12 h post-GVBD. (c) The proportion of overriding MI arrest was recorded in control and JB3-22 treated oocytes. Data were presented as mean percentage (mean ± SE) of at least three independent experiments. *$P < 0.05$, **$P < 0.01$.

cultured *in vitro* for 7 h to be maturated to MI and then processed for additional culture in the presence of Nocodazole (NOCO) alone or in combination with JB3-22. First polar body (PB1) extrusion rate was calculated 12 h after GVBD. The result showed that about 25% of control oocytes could abrogate MI arrest and extrude the first polar body (Figure 4(b)). However, about 40% of JB3-22 treated oocytes overriding MI arrest and displayed a remarkably increased pb1 extrusion rate (40.5 ± 1.6 verse 24.8 ± 2.7, control, P <0.01) (Figure 4(c)).

HDAC11 inhibition increased the acetylation levels of H4K16

The involvement of HDAC11 in activation of SAC and kinetochore functions prompted us to further explore the underlying mechanisms.

Properly modified acetylation level of H4 lysine 16 (H4K16) is crucial for kinetochore functions in mouse oocytes [12,24]. We thus wondered if HDAC11 inhibition disturbed the kinetochore functions by affecting the status of H4K16ac during oocyte meiosis. The immune-staining results showed that signals of H4K16ac were remarkably increased ($P < 0.05$) in JB3-22 treated MI and MII oocytes when compared with control (Figure 5(a, b)).

HDAC11 inhibition increased the acetylation levels of α-tubulin

HDAC11 was reported to be associate with HDAC6 in both the cytoplasm and nuclei [17]. The α-tubulin is an important substrate of HDAC6, HDAC6 could regulate microtubule stability and spindle assembly by modulating the acetylation status of α-tubulin [14,15]. We thus wondered if HDAC11 involved in regulating α-tubulin acetylation during mouse oocytes maturation. The immune-staining and

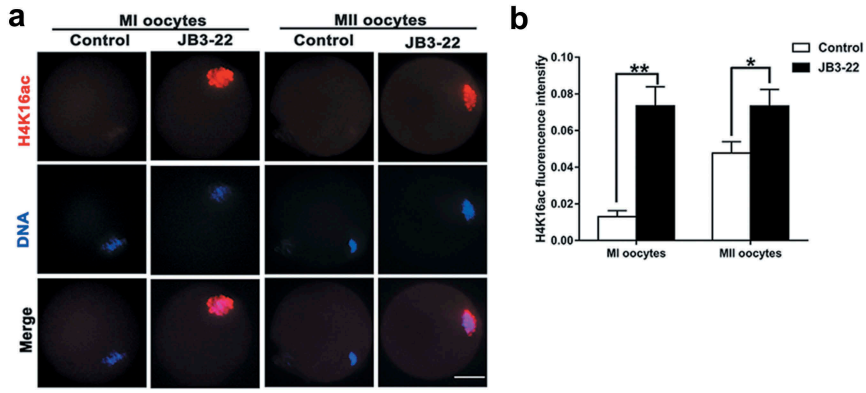

Figure 5. JB3-22 treatment increased acetylation level of H4K16.

(a) Images of acetylated H4K16 in control and JB3-22-treated MI and MII oocytes. Scale bar, 20 μm. (b) Quantitative analysis of the fluorescence intensity of acetylated H4K16 in control and JB3-22 treated MI and MII oocytes. The graph shows the mean ± SE of the results obtained in three independent experiments. *$P < 0.05$, **$P < 0.01$.

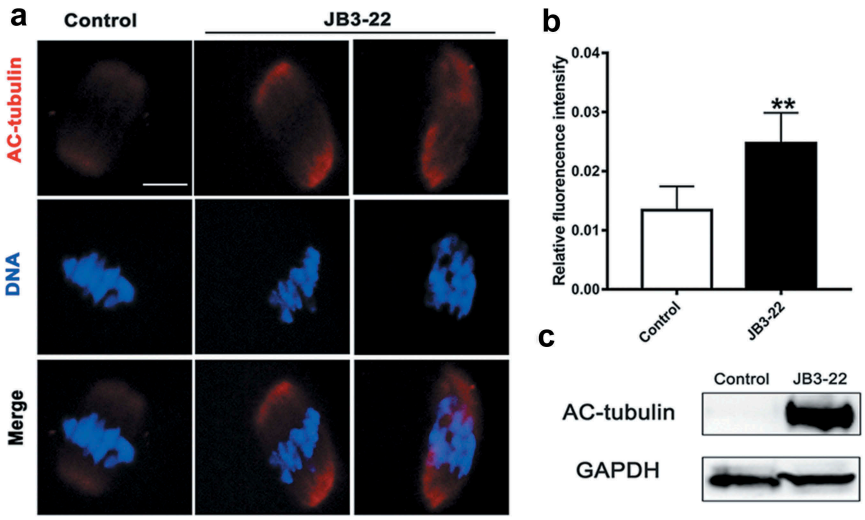

Figure 6. JB3-22 treatment increased acetylation level of α-tubulin.

(a) Images of acetylated α-tubulin in control and JB3-22-treated MI oocytes. Scale bar, 5 μm. (b) Quantitative analysis of the fluorescence intensity of acetylated α-tubulin in control and JB3-22 treated MI oocytes. The graph shows the mean ± SE of the results obtained in three independent experiments. *$P < 0.05$, **$P < 0.01$. (c) Protein levels of AC-tubulin in control and JB3-22 treated oocytes were determined by western blotting.

western blot results showed that signals of acetylated α-tubulin (AC-tubulin) were remarkably increased ($P < 0.05$) in JB3-22 treated MI oocytes when compared with control (Figure 6(a–c)).

Discussion

In the present study, we demonstrate for the first time that HDAC11 had expression in mouse oocytes. Inhibition of HDAC11 by its specific inhibitor JB3-22 interrupted GVBD and maturation of oocytes, caused aberrant spindle/chromosome assembly, impaired K-MT attachment and SAC function. HDAC11 inhibition also elevated the acetylation of α-tubulin and H4K16.

HDAC11 is the sole member of HDAC IV family, sharing sequence similarity to both class I and II HDAC proteins [16]. Recently published studies showed that several members of class I and II HDACs were actively participating in mouse oocytes maturation [11,14]. However, whether HDAC11 participates in oocyte maturation is still unknown. In this study, we found that HDAC11 had expression in oocytes, and its expression decreased gradually from GV to MII oocytes. The meiotic maturation coupled fluctuation of HDAC11 levels suggested that this type of histone deacetylase may perform a direct function in regulating meiotic cell cycle progression of oocytes. Accurate alignment and segregation of chromosomes is a crucial event in meiosis [25]. Correct K-MT attachment is essential for the bi-polar chromosome movement during meiosis process [26]. Unstable K-MT would activate SAC to block the onset of anaphase [27,28]. Previous study reported that HDAC3 knockdown or HDAC6 inhibition could all result in impaired meiotic apparatus and meiosis arrest [13,14]. In our study, HDAC11 inhibition in oocytes disrupted meiosis progression, spindle assembly and chromosome alignment, impaired both K-MT attachment and SAC expression. Along with this, the SAC function was severely impaired after HDAC11 inhibition, as JB3-22 treatment induces the escape of MI arrest induced by nocodazole. Taken together, HDAC11 is essential for spindle/chromosome assembly, K-MT attachment and SAC activation.

HDAC11 is reported to be associated with HDAC6 in both the cytoplasm and nuclear [17]. The α-tubulin is an important substrate of HDAC6, HDAC6 could regulate oocyte maturation by decreasing the acetylation status of α-tubulin in mouse oocytes [14,15]. In our study, inhibition of HDAC11 also resulted in an increased level of acetylated α-tubulin. It is possible that HDAC11 together with HDAC6 could regulate acetylation of α-tubulin cooperatively in mouse oocytes. HDAC11 is capable of deacetylating a synthetic peptide derived from histone H4 [17]. Acetylation of H4K16 has been shown to participate in the establishment of functional kinetochores in mouse oocytes [29]. HDAC2 knock-out could significantly increase the acetylation of H4K16 [12]. We such wondered if the impaired K-MT attachment in HDAC11 inhibited oocytes was resulted from dyregulated H4K16 acetylation. Our results showed that H4K16 acetylation was significantly increased in HDAC11-inhibited oocytes. Above all, HDAC11 inhibition elevated acetylation of α-tubulin and H4K16, which may be the potential pathways how HDAC11 modulate meiotic apparatus assembly.

In conclusion, HDAC11 is an essential factor for oocyte maturation. HDAC11 is required for meiotic spindle formation, suitable attachment between spindle and kinetochores, as well as SAC function. HDAC11 promotes meiotic process and meiotic apparatus most likely though modulating acetylation status of α-tubulin and H4K16.

Materials and methods

Animals

All experiments were approved by the Animal Care and Use Committee of Jilin University, China and were performed in accordance with institutional guidelines. The 7–8 weeks female ICR mice were purchased from Liaoning Changsheng biotechnology co., Ltd (Liaoning, China).

Drugs and antibodies

JB3-22 (B1893-1) was purchased from Biovision (San Francisco, USA). Mouse monoclonal FITC-conjugated α-tubulin (F2168) was purchased from Sigma (St. Louis, USA); rabbit polyclonal anti-histone H4 (acetyl K16) (ab109463), goat polyclonal anti-BubR1 (ab28193), Alexa Fluora488 and Alexa

Fluora647 conjugated rabbit anti-human IgG H&L (ab150129 and ab236481) were purchased from Abcam (Cambridge, UK); rabbit monoclonal anti-Acetyl-α-Tubulin antibody (#5335) was purchased from Cell Signaling (Danvers, USA); human anti-centromere antibody (CA95617) was purchased from Antibodies Incorporated (Davis, USA); CoraLite594–conjugated goat anti-rabbit IgG (H + L) (SA0001304) was purchased from Proteintech (Wuhan, China).

Oocyte collection and culture

Mice were sacrificed by cervical dislocation for oocyte collection. Fully growing oocytes arrested at prophase of meiosis I were retrieved by manual rupturing follicles with 18 channels needle. The oocytes were then cultured in M16 medium (Sigma, M7292) under liquid paraffin oil at 37°C in an atmosphere of 5% CO_2 incubator for *in vitro* maturation. GVBD (Germinal Vesicle Breakdown), Prometaphase I (Pro-MI), MI (Metaphase I) and MII (Metaphase II) oocytes were collected at 4 h, 6 h, 7 h and 16-h culture for subsequent analysis.

RNA isolation and quantitative PCR (qPCR)

Total RNA was extracted by RNeasy Mini kit (Qiagen, Hilden, Germany) from mouse oocytes. qPCR was performed in 96-well optical reaction plates after synthesis of cDNA using TransScript All-in-One First-Strand cDNA Synthesis SuperMix for qPCR (Transgen Biotech, Beijing, China), the primer sequence used for HDAC11 was: forward primer: 5'–GTTTACAACCGCCACATC-3'; reverse primer: 5' – ACATTCCTCTCCACCTTC-3'. Each 20 μL PCR reaction included 10 μL of SYBR green premix, 0.5 μL of each forward and reverse primer (10 μM), 1 μL of cDNA, and 8 μL of ddH_2O. Amplification conditions were as follows: 30 s denaturation at 95°C, 40 cycles of PCR for the quantitative analysis (95°C for 5 s and 60°C for 30 s), a melt-curve analysis (95°C for 5 s, 60°C for 60 s, 95°C for 1 s), and a hold at 4°C. The relative expression of each gene was calculated using the $2^{-\Delta\Delta CT}$ method. The quantitative PCR analysis was performed three times per sample.

Immunofluorescence and confocal microscopy analysis

Oocytes were fixed with 4% paraformaldehyde for 30 min in the dark and then permeabilized with 1% Triton X-100/PBS (v/v) for 15 min at room temperature. After blocking with PBS containing 1% bovine serum albumin (BSA) for 1 h, oocytes were incubated with primary antibodies at 4°C overnight, followed by incubation with secondary antibodies for 1.5 h at 37°C. After staining with Hoechst 33342 (10 μg/mL) for 10 min, oocytes were transferred to slides and mounted using prolong Gold Antifade Mountant (Invitrogen, P36930). Fluorescence was detected on a fluorescent microscope (Nikon, Tokyo, Japan) or confocal microscope (LSM 8800; Zeiss, Oberkochen, Germany). Fluorescence intensity was analyzed using ImageJ software (National Institutes of Health).

For kinetochore analysis, oocytes were immunolabeled with CREST as previously described [30]. Briefly, MI oocytes were treated on ice for 10 min, then fixed for 30 min and blocked at 4°C overnight, After permeation, the oocytes were incubated with primary antibodies at 37°C for 1 h, followed by incubation with secondary antibodies for 1 h at 37°C. Nuclear status was stained with Hoechst 33342 (blue) for 10 min. Fluorescence was detected on a confocal microscope (LSM 8800; Zeiss, Oberkochen, Germany).

Western blot analysis

A total of 300 oocytes were lysed in 10μL RIPA buffer (Beyotime, China) containing protease inhibitors and boiled for 5 min. Total oocyte proteins were subjected to electrophoresis on a 10% SDS-PAGE gel and transferred onto PVDF membranes, which were pretreated with methanol. The membranes were blocked in TBST containing 5% low fat dry milk for 1 h at room temperature. After three times PBST washing, the membranes were incubated with primary antibodies for acetylated α-tubulin (1:1000) and GAPDH (1:2000, 60,004–1, Proteintech) at 4°C overnight. Then, the membranes were incubated with HRP-conjugated secondary antibodies for 2 h at room temperature. Chemiluminescence was detected with ECL (Thermo, USA) and protein bands were visualized by Tanon-3900 (Tanon, China).

Statistical analysis

Data were analyzed by paired-samples *t*-test for comparisons. Both data analysis and graphics drawing were done using GraphPad Prism 5.0 software (Graphpad Software, San Diego, CA, USA). All data were expressed as mean ± SE. **P* value < 0.05 was considered to be statistically significant, ***P* value < 0.01 was considered to be extremely significant.

Disclosure statement

No potential conflict of interest was reported by the authors.

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