1 | INTRODUCTION

Advanced maternal age in mammals is associated with reduced fertility. Reproductive capacity in women declines dramatically beyond the mid-30s (Hamatani et al., 2004; Hassold & Hunt, 2001). In mice, there is an increased frequency of aneuploidy embryos and fetuses with maternal age (Golbus, 1981; Pan, Ma, Zhu, & Schultz, 2008). Emerging evidence suggests that poor oocyte quality is a critical factor mediating the effects of aging on female fertility (Keefe, Kumar, & Kalmbach, 2015; Volaricik et al., 1998). In mammals, the oocytes enter meiosis during the fetal period and their development arrests in the dictyate of prophase until they resume maturation just prior to ovulation at the reproductive age (Kurahashi et al., 2012). It is worth noting that this meiotic process is error prone. Oocytes with the wrong number of chromosomes give rise to aneuploid embryos following fertilization, which in humans is a major cause of pregnancy loss and developmental disabilities (Hassold & Hunt, 2001). Recently, it has been demonstrated that aged oocytes exhibit substantially altered spindle microtubule dynamics, resulting in kinetochore–microtubule attachment defects and chromosome segregation errors (Holubcova, Blayney, Elder, & Schuh, 2015; Nakagawa & FitzHarris, 2017).

Mammalian genomes encode 11 proteins of the classical histone deacetylase family (HDAC1-11) (Yang & Seto, 2008). These proteins are grouped into class I, II, and IV, with class II being further divided into two subclasses (IIa and IIb), based on their homology to yeast Rpd3/Hda1. HDACs play roles in numerous biological processes largely through their influence on transcription by modulating the acetylate
state of histones or transcription factors (Haberland, Montgomery, & Olson, 2009). HDAC3, as a member of class I, was found to function in stem cell self-renewal in a transcription-independent manner (Li et al., 2006). Accumulated evidence demonstrated that HDAC3 is required for normal mitotic progression through the interaction with Aurora B kinase (Eot-Houllier, Fulcrand, Watanabe, Magnaghi-Jaulin, & Jaulin, 2008; Fadri-Moskwik et al., 2012; Li et al., 2006). Intriguingly, we recently reported that HDAC3 depletion adversely influences meiotic maturation, especially spindle assembly and chromosome organization (Li et al., 2017), similar to the phenotypes of aged oocytes. HDAC3 has been shown to modulate the acetylation state of different substrates in multiple cell lines. For example, in an in vitro reconstituted chromatin system, an HDAC3-containing protein complex selectively deacetylated histone H3 (Vermeulen et al., 2004). Blocking HDAC3 activity could dramatically alter the tubulin acetylation in the human prostate cancer cells (Bacon et al., 2015). In the present study, we identify a substantial reduction of HDAC3 protein in oocytes from old mice. Notably, overexpression of HDAC3 is capable of alleviating the meiotic defects in oocytes from old mice. These findings indicate that HDAC3 insufficiency in the oocyte may represent a connection between oocyte quality and reproductive aging.

2 | RESULTS

2.1 | Reduced HDAC3 expression in oocytes from old mice

Given that the oocytes depleted of HDAC3 displayed the similar phenotypes as those from aged mice (Li et al., 2017), we decided to determine the HDAC3 expression in oocytes from young (3 weeks of age) and old (42 weeks of age) mice by Western blot analysis. As shown in Figure 1a-b, a remarkable reduction of HDAC3 protein was detected in germinal vesicle (GV) stage oocytes from old mice compared to that from young mice. Meanwhile, we also evaluated the HDAC3 expression and distribution in oocytes via

**FIGURE 1** Reduced expression of HDAC3 protein in oocytes from old mice. (a) Representative Western blots showing the HDAC3 expression in oocytes from young and old mice (100 fully grown GV oocytes per lane). (b) Quantification of Western blot results, with actin as a loading control. (c) Confocal sections of young and old oocytes stained with HDAC3 antibody (green) and counterstained with propidium iodide (red) for DNA. Arrowheads indicate the accumulated HDAC3 signal. (d) Quantification of HDAC3 immunofluorescence (n = 23 biologically independent oocytes for young; n = 27 biologically independent oocytes for old). Scale bars: 20 µm. (e) Representative Western blots showing the HDAC3 expression in oocytes cultured in vitro for 0 h, 8 h, and 12 h. *p < .05 versus controls.
immunostaining coupled with confocal microscopy. As shown in Figure 1c-d, there was no apparent alteration in the distribution pattern of HDAC3 between young and old oocytes. However, the average intensity of HDAC3 signal was significantly decreased in old oocytes relative to young cells. In addition, we found that the levels of HDAC3 protein in different stages of oocytes are comparable when cultured in vitro (Figure 1e), indicating the absence of fluctuation in HDAC3 expression during oocyte maturation.

2.2 HDAC3 overexpression alleviates the meiotic defects in old oocytes

To check whether the HDAC3 reduction contributes to the phenotypes of aged oocytes, we conducted the overexpression experiments through the microinjection of cRNA encoding HDAC3 into fully grown old oocytes (Figure 2a). As shown in Figure 2b, immunoblotting verified that exogenous HDAC3 protein was efficiently expressed in oocytes. Spindle/chromosome disorganization was frequently observed in old oocytes (Figure 2c-d), displaying the scattered chromosomes apart from the metaphase plate. Of note, ectopic expression of HDAC3 ameliorated these meiotic defects in old oocytes. Furthermore, to determine whether overexpression of HDAC3 in old oocytes could also prevent the generation of aneuploid eggs, we analyzed the karyotype of matured oocytes by chromosome spreading. As shown in Figure 2e-f, maternal aging induced about a threefold increase in incidence of aneuploid eggs compared to controls. Remarkably, the elevated HDAC3 expression in old oocytes significantly decreased the aneuploidy production. Altogether,
the results indicate that loss of HDAC3 is one of potential pathways mediating the effects of maternal aging on oocyte quality.

2.3 | Elevated acetylation levels of tubulin in old oocytes

Tubulin is one of the most abundant nonhistone proteins that is subjected to acetylation, which occurs on lysine (K) 40 of α-tubulin subunit (Zilberman et al., 2009). We previously demonstrated that HDAC3 modulates spindle/chromosome organization in oocytes by maintaining the hypoacetylation state of tubulin (Li et al., 2017). Herein, the reduced HDAC3 expression in old oocytes prompted us to ask whether the acetylation status of tubulin was altered accordingly. To address this question, MII oocytes were isolated from young and old mice. By performing Western blot and immunostaining analysis, we found that the acetylation level of tubulin‐K40 was markedly increased in old oocytes as compared to young oocytes (Figure 3a‐d). This observation implies that tubulin acetylation may be involved in the deficient meiotic apparatus in oocytes from old mice.

2.4 | Acetylation of tubulin‐K40 functions in kinetochore–microtubule interaction during oocyte meiosis

To test whether tubulin acetylation affects meiotic structure in oocytes, we constructed the site-specific mutants (K-to-Q and K-to-R) targeting lysine 40 (K40) of tubulin, and then the mRNA encoding the tubulin mutants was injected into fully grown oocytes for analysis. As shown in Figure 4a‐b, we found that acetylation-mimetic mutant K40Q resulted in almost threefold increase in spindle/chromosome defects compared to WT control, whereas K40R had little effects on meiotic apparatus.

Coordination between spindle maintenance and chromosome movement largely relies on kinetochore–microtubule (K-MT) interaction (Prosser & Pelletier, 2017). Hence, we further examined the effects of tubulin acetylation on K-MT attachment during meiosis. For this purpose, metaphase oocytes were immunolabeled with CREST to detect kinetochores and stained with anti-α-tubulin-FITC-conjugated antibody to visualize microtubules. As shown in Figure 4c, the majority of normal oocytes presented amphitelic attachment (each kinetochore attached to one of the poles). However, by performing quantitative analysis (Figure 4d), we found that the proportion of misattachments and loss attachment was significantly increased in oocytes overexpressed K40Q mutant in comparison with K40R oocytes. These erroneous K-MT attachments would induce unstable chromosome biorientation, causing the abnormal meiotic apparatus in oocytes. Collectively, these results strongly indicate that tubulin-K40 acetylation controlled by HDAC3 participates in the assembly of meiotic structure in oocytes via maintaining the proper K-MT interaction.

2.5 | Tubulin-K40R mutant ameliorates the meiotic defects in oocytes from old mice

Given the loss of HDAC3 and hyperacetylation of tubulin in old oocytes, we next checked whether the deacetylation-mimetic mutant of tubulin could ameliorate their phenotypic defects. To this end, tubulin-K40R mutant was microinjected into fully grown old oocytes and then in vitro matured for evaluating spindle/chromosome organization (Figure 5a). In comparison with controls, K40R significantly lowered the proportion of abnormal spindle/chromosomes and K-MT misattachments in old oocytes (Figure 5b-d). This finding suggests that nonacetylated tubulin-K40R is capable of partly rescuing the deficient phenotypes of aged oocytes.

Cells have a safety mechanism known as the spindle assembly checkpoint (SAC) to ensure that chromosomes have time to correctly line up on the spindle before the cell can divide (Overlack et al., 2015). Considering the involvement of tubulin acetylation in K-MT attachments, we further examined whether it affects
the SAC system in oocytes. To test this possibility, we analyzed the SAC activity during oocyte meiosis by immunolabeling of BubR1 (budding uninhibited by benzimidazole-related 1), a core component of the SAC system (Sudakin, Chan, & Yen, 2001). As shown in Figure 5e–f, BubR1 was localized to the unattached kinetochores at premetaphase I stage in normal oocytes, but was lost when kinetochores are properly attached to microtubules at metaphase I; however, BubR1 signals on the kinetochores in old oocytes at metaphase I stage (MI; culture for 8 hr) were markedly elevated as compared to the counterparts from young mice, indicative of the activation of SAC. Of note, forced expression of tubulin-K40R mutant in aged oocytes could significantly reduce the BubR1 signals on metaphase chromosomes. Taking together, tubulin acetylation is essential for maintaining the meiotic structure in oocytes probably by modulating the K-MT-based SAC system.

**FIGURE 4** Hyperacetylation of tubulin-K40 impairs kinetochore-microtubule attachments during oocyte meiosis. (a) WT, WT + K40R, WT + K40Q oocytes were stained with α-tubulin antibody to visualize spindle (green) and counterstained with PI to visualize chromosome (red). Arrows point to the misaligned chromosomes and arrowheads indicate the disorganized spindle. Scale bars: 20 µm. (b) Quantification of WT, WT + K40R, WT + K40Q oocytes with spindle/chromosome defects. (c) WT, K40Q and K40R mutant cRNA were microinjected into fully grown oocytes for analysis. Metaphase oocytes were stained with CREST for kinetochores (purple), anti-tubulin antibody for microtubules (green), and Hoechst 33,342 for chromosome (blue). Representative confocal images are shown. Scale bars: 5 µm. (d) Quantitative analysis of K-MT misattachments in WT (n = 16), K40R (n = 18), and K40Q (n = 13) oocytes. Attachment of kinetochores to microtubules was assessed through examination of the full series of Z-axis focal planes. Kinetochores in regions where fibers were not easily visualized were not included in the analysis. Scale bars: 20 µm. *p < .05 versus controls.
Among numerous HDACs, HDAC3 is ubiquitously expressed and conserved in a wide range of species (Ishii, Kurasawa, Wong, & Yu-Lee, 2008). HDAC3 was found in the nucleus and cytoplasm of different cell types (Longworth & Laimins, 2006; Takami & Nakayama, 2000). It has been reported that HDAC3 could form a well-characterized protein complex with the NCoR (nuclear receptor co-repressors) or homologous SMRT (silencing mediator of retinoic and thyroid receptors) to control the transcriptional activity (Bacon et al., 2015; Karagianni & Wong, 2007). Longworth et al. also reported that HDAC3 localizes to the plasma membrane and forms a complex with c-Src to regulate its activity in HFK + 31 cells (Longworth & Laimins, 2006). In addition, HDAC3 was detected over the spindle in HeLa cells and mouse 3T3 fibroblasts (Ishii et al., 2008). Similarly, we found HDAC3 resides in the cytoplasm of mouse oocytes, with accumulated signals on the meiotic spindle region, promoting the assembly of meiotic apparatus (Li et al., 2017).

It has been well documented that oocytes recovered from old females show a series of changes in multiple nuclear and cytoplasmic structures (Miao, Kikuchi, Sun, & Schatten, 2009). For example, the distribution of cortical granules (CGs) altered dramatically and CG contents became swollen in oocytes from old females (Díaz & Esponda, 2004). Mitochondrial DNA (mtDNA) copy number and function are reduced in eggs from aged mice after both in vivo and in vitro maturation (Pasquariello et al., 2019). In parallel with these changes, HDAC3 expression and activity in oocytes from old females have been reported to be altered (Li et al., 2017).

**3 | DISCUSSION**

Among numerous HDACs, HDAC3 is ubiquitously expressed and conserved in a wide range of species (Ishii, Kurasawa, Wong, & Yu-Lee, 2008). HDAC3 was found in the nucleus and cytoplasm of different cell types (Longworth & Laimins, 2006; Takami & Nakayama, 2000). It has been reported that HDAC3 could form a well-characterized protein complex with the NCoR (nuclear receptor co-repressors) or homologous SMRT (silencing mediator of retinoic and thyroid receptors) to control the transcriptional activity (Bacon et al., 2015; Karagianni & Wong, 2007). Longworth et al. also reported that HDAC3 localizes to the plasma membrane and forms a complex with c-Src to regulate its activity in HFK + 31 cells (Longworth & Laimins, 2006). In addition, HDAC3 was detected over the spindle in HeLa cells and mouse 3T3 fibroblasts (Ishii et al., 2008). Similarly, we found HDAC3 resides in the cytoplasm of mouse oocytes, with accumulated signals on the meiotic spindle region, promoting the assembly of meiotic apparatus (Li et al., 2017).

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observations, Nakagawa et al. found that spindle microtubule dynamics altered substantially in old oocytes, resulting in transiently multipolar spindles that predispose the oocytes to missegregation of intact sister chromatid pairs (Nakagawa & FitzHarris, 2017). However, the underlying molecular details remain to be elucidated. In the present study, we identified a reduction of HDAC3 protein in oocytes from old mice (Figure 1). Importantly, we noted that overexpression of HDAC3 in old oocytes could partially rescue the spindle/chromosomes defects and lower the incidence of aneuploidy eggs (Figure 2). Therefore, these findings support the conclusion that loss of HDAC3 is an important factor contributing to the compromised oocyte quality of aged mice, specifically to failure to assemble the meiotic apparatus.

Microtubules are subject to a remarkable number of post-translational modifications. Thirty years ago, the conserved ε-amino group of lysine 40 of the N-terminal domain of the α-tubulin was identified as the site of acetylation (LeDizet & Piperno, 1987). The association of acetylation with long-lived microtubules indicated that stable microtubules tend to be acetylated (Schatten et al., 1988). Reed et al. further showed that loss of α-tubulin acetylation influences the binding and motility of kinesin-1 in vitro (Reed et al., 2006). Like other post-translational modifications of tubulin, acetylation on lysine 40 is under the control of balanced enzyme activities (acetyltransferases and deacetylases). αTAT1 was identified to be the major α-tubulin acetyltransferase (Kalebic et al., 2013; Shida, Cueva, Xu, Goodman, & Nachury, 2010). Recently, Bacon et al. found that blocking HDAC3 activity modulates tubulin acetylation in the human prostate cancer line PC3 (Bacon et al., 2015). Likewise, we previously showed that the acetylation levels of α-tubulin were dramatically increased in mouse oocytes depleted of HDAC3 (Li et al., 2017). In line with this observation, here we found the elevated acetylation of tubulin in old oocytes with lowered HDAC3 expression (Figure 3). Moreover, our data showed that nonacetylated tubulin-K40R is capable of partly rescuing the deficient phenotypes of aged oocytes (Figure 5). These results suggest that HDAC3-dependent tubulin deacetylation functions as a protective mechanism in oocytes, which is aberrantly blunted in the aged mouse model.

Microtubule stability is regulated in part by a heterogeneous family of proteins that bind to tubulin subunits of microtubules. Related to the functions of microtubules, cyclin B1 interacts with microtubule-associated proteins (MAPs) to regulate cell cycle progression (Ookata, Hisanaga, Okano, Taghizadeh, & Kishimoto, 1992). On the other hand, the gradual increase in cyclin B1 levels and CDK1 activity acts as a timing mechanism to modulate the formation of stable K-MT interaction in oocytes (Davydenko, Schultz, & Lampson, 2013). Herein, we found that the acetylation-mimetic mutant tubulin-K40Q induces erroneous K-MT attachments in oocytes (Figure 5). In combination with the differential meiotic progression between young and old oocytes (Eichenlaub-Ritter & Boll, 1989), we propose that advanced maternal age induces the loss of HDAC3 in oocytes, likely through elevating tubulin acetylation, results in kinetochore–microtubule misattachments, thereby contributing to the meiotic defects and aneuploidy generation (Figure 5g). In addition, SIRT2 reduction has recently been reported to contribute to oocyte aging by influencing acetylation status of histone H4K16 (Zhang et al., 2014). Therefore, the present study cannot rule out that other pathways might be regulated by HDAC3 to affect meiotic activity in oocytes.

4 | MATERIALS AND METHODS

All chemicals and culture media were obtained from Sigma unless otherwise specified.

4.1 | Animals

42-week-old female ICR mice were used as a model of reproductive aging, 3-week-old female mice were used as a control. All animal protocols were approved by the Animal Care and Use Committee of Nanjing Agricultural University, and all experiments were conducted in accordance with the guidelines of the local animal ethical committee and the Animal Care and Use Committee of Nanjing Agricultural University.

4.2 | Antibodies

Rabbit polyclonal anti-HDAC3 antibodies were purchased from Santa Cruz Biotechnology (Cat#: sc-376957; 1:150); Mouse polyclonal anti-acetyl-tubulin (Lys-40) antibodies were purchased from Sigma (Cat#: T7451; 1:200); Mouse monoclonal FITC-conjugated anti-α-tubulin antibodies were purchased from Sigma (Cat#: F2168; 1:500). Mouse monoclonal anti-HDAC3 antibodies were purchased from Cell Signaling Technology (Cat#: 3949T; 1:1,000); human anti-centromere CREST antibody was purchased from Antibodies Incorporated (Davis, CA, USA; Cat#: 15–234; 1:500); Cy5-conjugated donkey anti-human IgG and FITC-conjugated donkey anti-goat IgG were purchased from Jackson ImmunoResearch Laboratory (Cat#: 709–605–149 and 705–095–147; 1:500); goat polyclonal anti-BubR1 antibodies and mouse monoclonal anti-Myc tag antibody were purchased from Abcam (Cat#: ab28193 and ab18185; 1:250); FITC-conjugated goat anti-rabbit IgG purchased from Thermo Fisher Scientific (1:300).

4.3 | Collection and culture of oocytes

Female mice were injected with 5 IU PMSG to stimulate follicular development. Mice were euthanized by cervical dislocation 48 hr after the PMSG priming. Cumulus-oocyte complexes (COCs) were isolated by rupturing of antral ovarian follicles with sterile needles. Cumulus cells were removed by repeatedly pipetting, and fully grown GV oocytes were cultured in M16 medium under mineral oil at 37°C in a 5% CO2 incubator.

4.4 | cRNA synthesis and overexpression experiments

Total RNA was extracted from 50 denuded oocytes using the Arcturus PicoPure RNA Isolation Kit (Applied Biosystems), and cDNA was generated using Quantitect Reverse Transcription Kit
were stained with Hoechst 33,342. Kinetochores were labeled with CREST and chromosomes were examined under a laser scanning confocal microscope (LSM 710). Fluorescent slides in a drop of antifade medium (Vectashield) and then examined.

Body for 1 hr at room temperature. Samples were mounted on glass slides in 2× Laemmli sample buffer. Samples were denatured at 100°C for 5 min, and then frozen at −20°C until use. Lysates were separated by 10% SDS-PAGE and proteins transferred to PVDF membrane. Membranes were blocked with 5% nonfat milk in Tris-buffered saline containing 0.1% Tween-20 (TBST) for 1 hr at room temperature and then probed with primary antibodies (Myc antibody, 1:1,000; HDAC3 antibody, 1:1,000) at 4°C overnight. After multiple washes in TBST and incubation with HRP-conjugated secondary antibodies, the protein bands were visualized using an ECL Plus Western Blotting Detection System. β-actin was used as a loading control.

4.8 | Statistical analysis

Experiments were performed at least in triplicate. Data are presented as means ± SD, unless otherwise stated. Differences between two groups were analyzed by Student’s t test. Multiple comparisons between more than two groups were analyzed by one-way ANOVA test using Prism 5.0. p < .05 was considered to be significant.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

Y.H. and L.G. designed research; Y.H., X.L., M.G. performed research; L.G. and H.L. analyzed data; Y.H. and L.G. wrote paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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