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Changes in Histone Acetylation During Postovulatory Aging of Mouse Oocyte[1]

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ABSTRACT

Because some animals and human beings potentially engage in sexual activity at any day of the menstrual cycle, this may cause fertilization of postovulatory aged oocytes, which result in decreased potential of embryo development and longevity of offspring. To investigate the involvement of histone acetylation in the function of postovulatory aging, we examined the changes of histone acetylation by immunostaining with specific antibodies against various acetylated lysines on histones H3 and H4. We found that the acetylation levels of lysine 14 on histone H3 and lysines 8 and 12 on histone H4 in mouse oocytes were gradually increased during in vivo and in vitro postovulatory aging. Furthermore, the acetylation levels on these sites were markedly decreased or increased when the process of postovulatory aging was artificially delayed or accelerated, respectively. These results indicated that the gradual acetylation on some lysines of histones H3 and H4 is one of the phenomena in the process of postovulatory aging. Moreover, raising the level of histone acetylation by trichostatin A can accelerate the progression of postovulatory aging, suggesting that alteration of the acetylation on histones H3 and H4 can affect the progression of postovulatory aging in mouse oocytes.

aging, gamete biology, histone acetylation, mouse, oocyte development, postovulatory aging, trichostatin A

INTRODUCTION

Some mammalian species, especially some primates (including human beings), potentially engage in sexual activity at any day of the menstrual cycle. Ovulation and insemination may not be synchronized, resulting in the oocytes reaching the end of their life span [1]. It is well known that the metaphase II-arrested (MII) oocytes have a short fertilizable life span with a time-dependent decrease of their normal developmental competence after ovulation. For example, mouse oocytes can be fertilized in vivo for about 15 h after ovulation [2].

Deterioration occurring in the ovulated mature oocyte during prolonged culture is called postovulatory aging, and those oocytes in which aging has occurred but have not degenerated are called aged oocytes [3]. Aging not only decreases the potential of oocytes for fertilization and embryo development, but also gives rise to offspring suffering from retarded sensorimotor integration during preweaning development, increased spontaneous activity, higher emotionality [4], and decreased reproductive fitness and longevity [1].

Although the molecular changes occurring in the aged oocyte cytoplasm and the mechanisms inducing these phenomena are not well understood, mitochondrial dysfunction and reduction of the maturation promoting factor (MPF) may be involved in such a process. In aged oocytes, morphological abnormalities of mitochondria were observed [5]. The ATP content and mitochondrial membrane potential decrease steadily with extended culture time in oocytes [6, 7]. Such generalized damage to oocyte mitochondria increases the probability that the resulting offspring carry a subpopulation of defective mitochondria, decreased fecundity, and shortened life expectancy [8].

Moreover, the gradual decrease in MPF activity during aging is one of the reasons for oocyte aging. Regulation of MPF activity depends upon the association of CDC2 kinase, catalytic subunit, and cyclin B, regulatory subunit. Inactivation of MPF is caused by proteolysis of cyclin B [9] and phosphorylation of CDC2 [10]. A previous study has shown that artificially regulating MPF activity by phosphorylation or dephosphorylation of CDC2 in porcine postovulatory aging oocytes can promote or delay aging, respectively [3].

The acetylation of nuclear core histones is thought to play important roles in various cellular functions [11–13]. The acetylation-deacetylation switch depends on different physiological conditions, and the balance between these modifications is achieved through the action of enzymes named histone acetyltransferases (HATs) and histone deacetyltransferases (HDACs). The findings that HDACs can regulate the life span of different organisms have shed new light on the underlying mechanism of aging. Overexpression of SIR2, a NAD^+-dependent histone deacetylase, extends yeast and *Caenorhabditis elegans* life span [14], whereas deletion of a different HDAC (RPD3) also extends life span. Studies have shown that these two HDACs deacetylate different lysine residues on the N-terminal tails of histones. SIR2 can specifically deacetylate lysines 9 and 14 of histone H3 and lysine 16 of histone H4 [15], and RPD3 deletion preferentially influenced histone H4 lysine residues 5 and 12 [16]. Alteration in the pattern of gene expression involved in longevity by changing the level and the pattern of histone acetylation may be an important factor in determining the longevity of animals [17].

In 3-wk-old mouse oocytes, histones H3 and H4 are deacetylated globally at MII by HDAC activity [18], but in 10-mo-old mouse oocytes, histones remain acetylated [19]. In addition, inhibition of meiotic histone deacetylation can induce aneuploidy in fertilized mouse oocytes, which results in embryonic death in utero at an early stage of development

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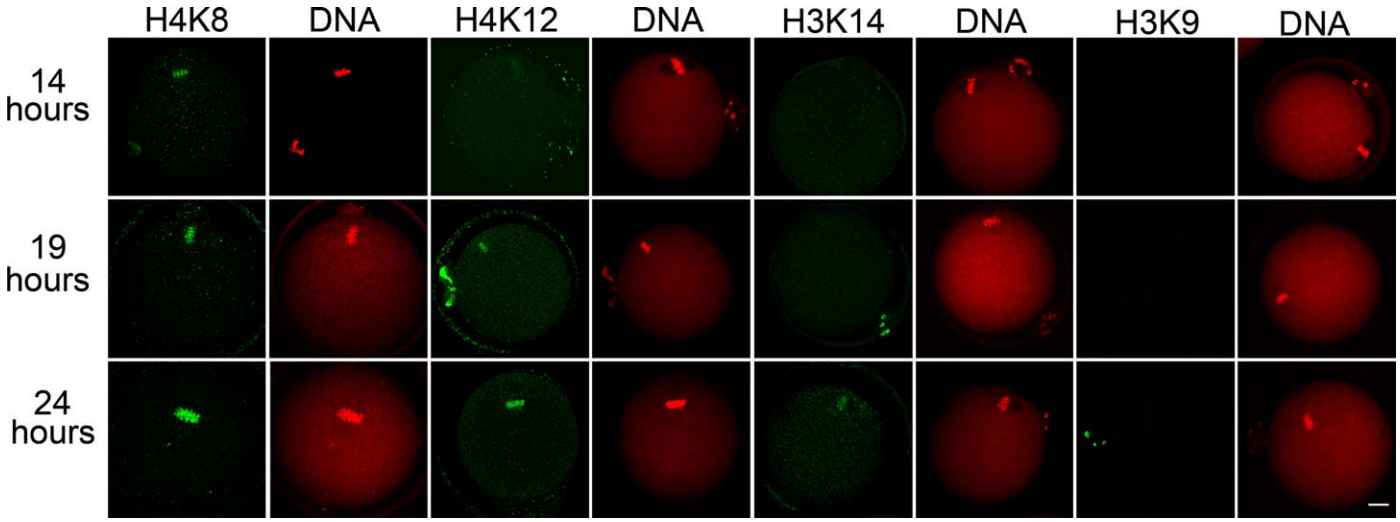


FIG. 1. Acetylation of lysine 14 on histone H3 and lysines 8 and 12 on histone H4 during postovulatory aging of mouse oocytes. Oocytes were immunostained with specific antibodies against acetylated lysine 14 on histone H3 (AcH3K14 [labelled H3K14]) and lysines 8 and 12 on histone H4 (AcH4K8 and AcH4K12 [labelled H4K8 and H4K12 respectively]). 14 h, oocytes at 14 h after hCG injection; 19 h, oocytes at 19 h after hCG injection; 24 h, oocytes at 24 h after hCG injection. AcH3K14, AcH4K8, and AcH4K12, green; DNA, red. Bar = 20 μm.

[19]. However, the changes and functions of histone acetylation in the process of postovulatory aging in mouse oocytes are unknown.

In the present study, to investigate the involvement of histone acetylation in the function of postovulatory aging, we examined the changes in the acetylation patterns of various lysine residues in histones H3 and H4 during postovulatory aging of the mouse oocyte. Furthermore, we investigated whether the process of postovulatory aging was changed when the levels of histone acetylation were altered in mouse oocytes by culturing the oocytes with trichostatin A (TSA).

MATERIALS AND METHODS

Animals

We used Kunming white mice as oocyte donors. All animals were maintained in accordance with the Animal Experiment Standard of Institute of Zoology, Chinese Academy of Sciences. Unless otherwise noted, all chemicals used in this study were purchased from Sigma-Aldrich.

Collection and Culture of Mouse Oocytes

For studies of in vivo postovulatory aged oocytes, oocytes were flushed at 14, 19, and 24 h after injection of hCG from the oviducts of 4- to 6-wk-old female Kunming white mice that had been injected i.p. with 10 IU of eCG (Tianjin Animal Hormone Factory, Tianjin, China), followed 48 h later by 10 IU of hCG (Tianjin Animal Hormone Factory). Oocytes were collected in M2 medium, and cumulus cells were removed with 0.1% hyaluronidase for 3–5 min in the same solution.

For studies of in vitro postovulatory aged oocytes, oocytes were flushed at 14 h post-hCG and cultured for 19–24 h after hCG injection in M16 medium under a humidified atmosphere of 5% CO_2 and 95% air at 37°C. At the end of the culture, cumulus cells were removed, and oocytes were immediately used as indicated below.

Activation and Assessment of Activated Oocytes

Oocytes were treated with 7% (v/v) ethanol in M2 medium for 5 min at room temperature and then washed three times and cultured in M16 containing 2 mM 6-dimethylaminopurine (6-DMAP) for 5 h. At the end of culture, oocytes were observed under the microscope for parthenogenetic activation. Oocytes with a pronucleus or pronuclei were considered activated. At least 30 oocytes were evaluated each replicate, and three replicates were performed.

Treatment of MII Oocytes with 6-DMAP, TSA, or Caffeine

Oocytes, flushed at 14 h post-hCG, were cultured for 19 h post-hCG in M16 medium containing 1 mM 6-DMAP or 100 nM TSA, or they were cultured for 24 h post-hCG in M16 medium with 8 mM caffeine. For control treatments, oocytes were cultured in M16 containing 0.05% dimethyl sulfoxide.

Indirect Immunofluorescence and Scanning Confocal Microscopy

The oocytes were immunostained with antibodies against acetylated lysines 9 (Cell Signaling Technology) and 14 (Upstate Biotechnology) of histone H3 (AcH3K9 and AcH3K14), lysines 5, 8, 12 (Upstate Biotechnology), and 16 (Santa Cruz Biotechnology) of histone H4 (AcH4K5, AcH4K8, AcH4K12, and AcH4K16), and alpha-tubulin (Sigma-Aldrich). Instrument settings were kept constant for each replicate. Each developmental panel was repeated three times, and at least 20 oocytes were evaluated each time. The details were described previously [20].

Statistical Analysis

For treated and control groups, data were compared statistically by the Student *t*-test. Statistical significance was evaluated at $P < 0.05$.

RESULTS

Histone Acetylation During Postovulatory Aging of MII Oocytes

The acetylation levels of various lysine residues on histones H3 and H4 were examined in in vivo and in vitro postovulatory aging of mouse oocytes at 14, 19, and 24 h after hCG injection. Immunocytochemistry with specific antibodies against AcH3K9, AcH3K14, AcH4K5, AcH4K8, AcH4K12, and AcH4K16 showed that the fluorescence signals for all of the antibodies, with the exception of a weak signal for AcH4K8, were absent from the oocytes at 14 h post-hCG, as described in a previous study [18]. With subsequent postovulatory aging, however, H4K12 was acetylated at 19 h post-hCG, and H3K14 was also acetylated at 24 h after hCG in in vivo and in vitro postovulatory aged oocytes. Moreover, intense fluorescence signals for AcH4K8 and AcH4K12 were gradually increased in the progression of postovulatory aging (Fig. 1). However, no fluorescence signals for AcH3K9, AcH4K5, and AcH4K16

TABLE 1. Changes in histone acetylation during postovulatory aging of mouse oocyte as shown by fluorescence signals.[a]

	In vivo (%)[b]			In vitro (%)[c]		
Histone/lysine	14 h	19 h	24 h	14 h	+5 h	+10 h
H3K9	− (100)	− (100)	− (100)	− (100)	− (100)	− (100)
H3K14	− (100)	− (100)	+ (87)	− (100)	− (100)	+ (84.8)
H4K5	− (100)	− (100)	− (100)	− (100)	− (100)	− (100)
H4K8	± (85.5)	+ (100)	+ (100)	± (82.9)	+ (100)	+ (100)
H4K12	− (77)	+ (100)	+ (100)	− (81)	+ (97)	+ (100)
H4K16	− (100)	− (100)	− (100)	− (100)	− (100)	− (100)

[a] Fluorescence signals are indicated as follows: intense (+), weak (±), and absent (−).
[b] Oocytes are flushed at 14, 19, and 24 h after hCG injection.
[c] Oocytes are flushed at 14 h after hCG injection, and then cultured for 5 or 10 h in M16.

were detected during postovulatory aging (Fig. 1; AcH4K5 and AcH4K16, data not shown). The acetylation states of various lysine residues of histones H3 and H4 during in vivo and in vitro postovulatory aging of mouse oocytes are summarized in Table 1.

6-DMAP Promotes Histone Acetylation in Mouse Oocytes During Postovulatory Aging

MII oocytes show a high activity of MPF, a complex of activated CDC2 and cyclin B that maintains the MII state for fertilization [21]. The gradual decrease of MPF activity during postovulatory aging is one of the reasons for oocyte aging. Moreover, regulation of MPF activity can manipulate oocyte aging to some extent in porcine [3] and mouse oocytes [22]. 6-DMAP, an in vitro protein kinase inhibitor, is shown to block the MPF activity by stimulating the tyrosine phosphorylation of CDC2 [23]. Compared with the control group, the activation rate, as a specific biomarker for oocyte aging [24, 25], in the oocytes cultured in M16 with 1 mM 6-DMAP for 5 h was significantly higher (78% vs. 49%, $P < 0.01$). Furthermore, we examined the changes of the acetylation levels in H3K14 and H4K12 and found that a signal for the anti-AcH3K14 or an intense signal for the anti-AcH4K12 existed in the 6-DMAP-treated oocytes (Fig. 2).

Caffeine Inhibits Histone Acetylation in Mouse Oocytes During Postovulatory Aging

It has been reported that caffeine can delay the progression of postovulatory aging in porcine oocytes [3] and mouse oocytes (data not shown). Compared with the control group, the activation rate of the oocytes cultured in M16 with 8 mM caffeine for 10 h was significantly decreased (82% vs. 35%, $P < 0.01$). Therefore, we proposed that caffeine could induce the changes in the histone acetylation patterns during the postovulatory aging. To confirm this hypothesis, the changes in the acetylation levels of H3K14 and H4K12 were examined. The oocytes, flushed at 14 h post-hCG, were cultured in M16 with or without 8 mM caffeine for 10 h. Compared with the control group, no signal for the anti-AcH3K14 or a weak signal for the anti-AcH4K12 was shown in the caffeine-treated oocytes (Fig. 3).

TSA Accelerates the Progression of Postovulatory Aging in Mouse Oocytes

We next investigated whether artificial modification of the status of histone acetylation by the inhibitor of HDAC could alter the progression of postovulatory aging in mouse oocytes. The TSA has been reported to be a highly specific inhibitor of HDACs [26]. The oocytes cultured in M16 with 100 nM TSA for 5 h were acetylated in H3K14 and H4K12 but not in H3K9 and H4K5 when these four sites were examined. The activation rate in the TSA-treated oocytes was significantly higher than in the control group (Fig. 4A). Furthermore, TSA resulted in aberrant spindles in the treated oocytes (Fig. 4B), due to the abnormal spindle increase in the aged oocyte [27].

DISCUSSION

In the present study, we demonstrated that the acetylation levels on H3K14, H4K8, and H4K12 in mouse oocytes were obviously increased during in vivo and in vitro postovulatory aging. Furthermore, the acetylation levels on these sites were markedly decreased or increased when the progression of postovulatory aging was artificially delayed or accelerated, respectively. In addition, raising the levels of histone

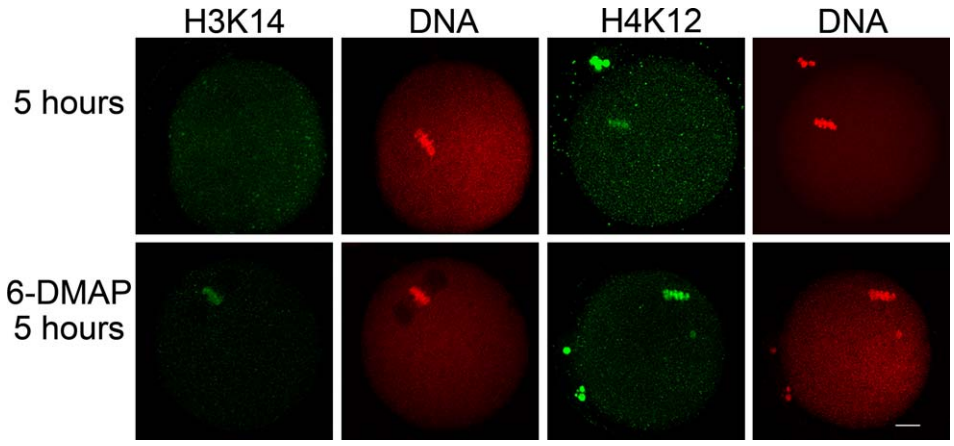


FIG. 2. Changes in the acetylation on lysine 14 of histone H3 and lysine 12 of histone H4 during postovulatory aging of mouse oocytes treated with 6-dimethylaminopurine (6-DMAP). Oocytes were immunostained with specific antibodies against acetylated lysine 14 on histone H3 (AcH3K14 [labelled H3K14]) and lysine 12 on histone H4 (AcH4K12 [labelled H4K12]). 5 h, oocytes were flushed at 14 h after hCG injection and then cultured for 5 h in M16 medium; 6-DMAP 5 h, oocytes were flushed at 14 h after hCG injection and then cultured for 5 h in M16 medium with 6-DMAP. AcH3K14 and AcH4K12, green; DNA, red. Bar = 20 μm.

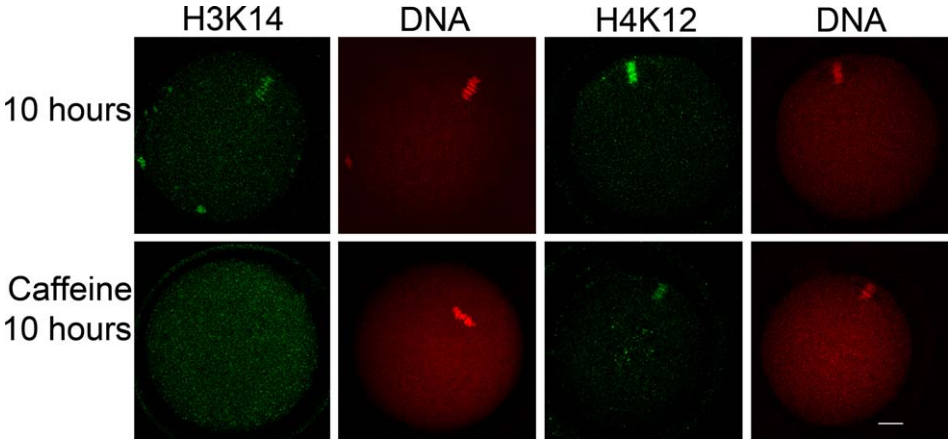


FIG. 3. Changes in the acetylation on lysine 14 of histone H3 and lysine 12 of histone H4 during the postovulatory aging of mouse oocytes treated with caffeine. Oocytes were immunostained with specific antibodies against acetylated lysine 14 on histone H3 (AcH3K14 [labelled H3K14]) and lysine 12 on histone H4 (AcH4K12 [labelled H4K12]). 10 h, oocytes were flushed at 14 h after hCG injection and then cultured for 10 h in M16 medium; caffeine 10 h, oocytes were flushed at 14 h after hCG injection and then cultured for 10 h in M16 medium with caffeine. AcH3K14 and AcH4K12, green; DNA, red. Bar = 20 μm.

acetylation by adding TSA in the culture medium can accelerate the progression of postovulatory aging in mouse oocytes.

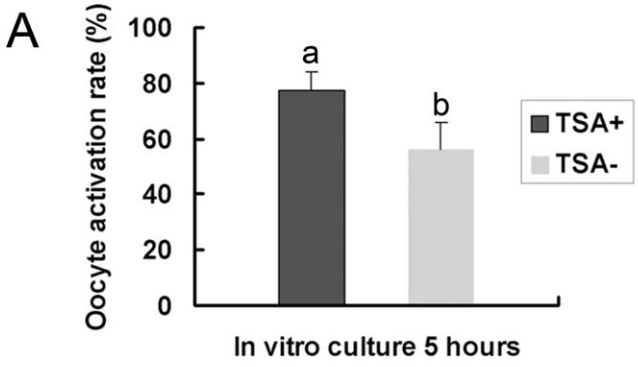
A previous study has shown that mouse oocytes at the germinal vesicle (GV) stage are acetylated at various lysine residues of histones H3 and H4 but deacetylated globally at meiosis because of the activities of HDACs and the absence of the HAT functions during the entire meiotic metaphase [18, 28]. With subsequent postovulatory aging, we found that histones H3 and H4 were acetylated at some lysine residues, suggesting that decreased histone deacetylation contributed to postovulatory aging in mouse oocytes. Moreover, the acetylation levels of histones H3 and H4 were markedly decreased or increased when the progression of postovulatory aging was artificially delayed or accelerated, respectively. These results indicate that the gradual acetylation on some lysines of histones H3 and H4 is one of the phenomena during postovulatory aging of the mouse oocyte.

The acetylation of histone H3 occurs initially at lysine 14 and then at lysine 23, lysine 18, and, eventually, lysine 9 [29], while the acetylation of histone H4 occurs initially at lysine 16 and then at lysine 12 or lysine 8 and eventually at lysine 5 [30]. Therefore, AcH3K9 and AcH4K5 reflect the hyperacetylated state in histones H3 and H4. During postovulatory aging, lysine residues 8 and 12 on histone H4 and 14 on histone H3 were gradually acetylated, but acetylation was not found in lysine residues 5 and 9. There may be two possible explanations. First, these results indicate that the level of histone acetylation is lower during postovulatory aging than in the GV stage, suggesting that the function of histone deacetylation decreases but does not disappear during postovulatory aging. Second, mouse oocytes were acetylated at some specific lysine residues on histones H4 and H3 during the postovulatory aging, because only lysines 12 and 14 were gradually acetylated, but lysines 5 and 9 kept deacetylation status during postovulatory aging, even when treated by TSA for 5 h when lysine residues 9 and 14 on histone H3 and 5 and 12 on histone H4 were examined.

The acetylation states of various lysine residues on histones H3 and H4 in postovulatory aged oocytes exhibited changes similar to those in the oocytes from old mice, except on H3K14, for which H3K14 was deacetylated in old mouse oocytes [19]. This discrepancy in the acetylation of H3K14 between maternal and postovulatory aging remains to be elucidated.

When comparing these two kinds of aged oocytes, we can find that there are many common phenomena: lower fertilization competence, polyspermy, chromosomal anomalies, high rates of DNA fragmentation, abnormal and retarded development of embryos or fetuses, and increased mortality [8, 31].

Oocytes in old mice are accompanied by distinct alterations in the pattern of gene expression [31]. We therefore proposed that the changes in histone acetylation, which involved the alteration of chromosomal structure and function, would be a



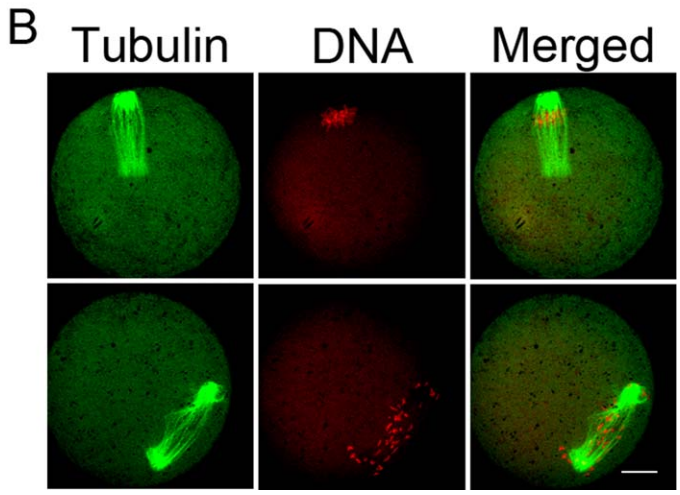


FIG. 4. Histone acetylation in metaphase II-arrested mouse oocytes treated with trichostatin A (TSA). Oocytes were flushed at 14 h after hCG injection and then cultured for 5 h in M16 medium with or without TSA (TSA+, TSA–). **A**) Oocytes treated with TSA showed a significantly higher parthenogenetic activation rate compared with control oocytes ($P < 0.05$, Student *t*-test; different letters denote significant differences). **B**) Oocytes treated with TSA showed aberrant spindles. Alpha-tubulin, green; DNA, red. Bar = 20 μm.

contributing factor in the postovulatory aging of the mouse oocyte. As expected, we confirmed that raising the level of histone acetylation with TSA could accelerate the process of postovulatory aging in this study. Similar phenomena are also observed in somatic cells. In previous studies, TSA has been shown to induce premature senescence in normal human fibroblasts [32, 33]. Moreover, a recent study has shown that TSA can selectively trigger the senescent phenomenon in presenescent cells [34]. However, it must be noted that we cannot exclude the possibility that caffeine, 6-DMAP, and TSA can also be specifically affecting the oocyte activation pathway without directly affecting oocyte aging.

Our findings indicate that the gradual acetylation on some lysines of histones H3 and H4 is one of the phenomena in the process of postovulatory aging in mouse oocytes. Moreover, raising the level of histone acetylation by TSA could accelerate the progression of postovulatory aging, suggesting that changes in the acetylation on histones H3 and H4 can affect the progression of postovulatory aging in mouse oocytes.

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REFERENCES

1. Tarin JJ, Perez-Albala S, Perez-Hoyos S, Cano A. Postovulatory aging of oocytes decreases reproductive fitness and longevity of offspring. Biol Reprod 2002; 66:495–499.
2. Marston JH, Chang MC. The fertilizable life of ova and their morphology following delayed insemination in mature and immature mice. J Exp Zool 1964; 155:237–251.
3. Kikuchi K, Naito K, Noguchi J, Shimada A, Kaneko H, Yamashita M, Aoki F, Tojo H, Toyoda Y. Maturation/M-phase promoting factor: a regulator of aging in porcine oocytes. Biol Reprod 2000; 63:715–722.
4. Tarin JJ, Perez-Albala S, Aguilar A, Minarro J, Hermenegildo C, Cano A. Long-term effects of postovulatory aging of mouse oocytes on offspring: a two-generational study. Biol Reprod 1999; 61:1347–1355.
5. Tarin JJ, Perez-Albala S, Cano A. Cellular and morphological traits of oocytes retrieved from aging mice after exogenous ovarian stimulation. Biol Reprod 2001; 65:141–150.
6. Chi MM, Manchester JK, Yang VC, Curato AD, Strickler RC, Lowry OH. Contrast in levels of metabolic enzymes in human and mouse ova. Biol Reprod 1988; 39:295–307.
7. Wilding M, Dale B, Marino M, di Matteo L, Alviggi C, Pisaturo ML, Lombardi L, De Placido G. Mitochondrial aggregation patterns and activity in human oocytes and preimplantation embryos. Hum Reprod 2001; 16:909–917.
8. Tarin JJ, Perez-Albala S, Cano A. Consequences on offspring of abnormal function in ageing gametes. Hum Reprod Update 2000; 6:532–549.
9. Norbury C, Nurse P. Animal cell cycles and their control. Annu Rev Biochem 1992; 61:441–470.
10. Kikuchi K, Naito K, Noguchi J, Shimada A, Kaneko H, Yamashita M, Tojo H, Toyoda Y. Inactivation of p34cdc2 kinase by the accumulation of its phosphorylated forms in porcine oocytes matured and aged in vitro. Zygote 1999; 7:173–179.
11. Kurdistani SK, Grunstein M. Histone acetylation and deacetylation in yeast. Nat Rev Mol Cell Biol 2003; 4:276–284.
12. Turner BM. Cellular memory and the histone code. Cell 2002; 111:285–291.
13. Vogelauer M, Rubbi L, Lucas I, Brewer BJ, Grunstein M. Histone acetylation regulates the time of replication origin firing. Mol Cell 2002; 10:1223–1233.
14. Hekimi S, Guarente L. Genetics and the specificity of the aging process. Science 2003; 299:1351–1354.
15. Imai S, Armstrong CM, Kaeberlein M, Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature 2000; 403:795–800.
16. Rundlett SE, Carmen AA, Kobayashi R, Bavykin S, Turner BM, Grunstein M. HDA1 and RPD3 are members of distinct yeast histone deacetylase complexes that regulate silencing and transcription. Proc Natl Acad Sci U S A 1996; 93:14503–14508.
17. Chang KT, Min KT. Regulation of lifespan by histone deacetylase. Ageing Res Rev 2002; 1:313–326.
18. Kim JM, Liu H, Tazaki M, Nagata M, Aoki F. Changes in histone acetylation during mouse oocyte meiosis. J Cell Biol 2003; 162:37–46.
19. Akiyama T, Nagata M, Aoki F. Inadequate histone deacetylation during oocyte meiosis causes aneuploidy and embryo death in mice. Proc Natl Acad Sci U S A 2006; 103:7339–7344.
20. Huang JC, Lei ZL, Shi LH, Miao YL, Yang JW, Ouyang YC, Sun QY, Chen DY. Comparison of histone modifications in in vivo and in vitro fertilization mouse embryos. Biochem Biophys Res Commun 2007; 354: 77–83.
21. Jones KT. Turning it on and off: M-phase promoting factor during meiotic maturation and fertilization. Mol Hum Reprod 2004; 10:1–5.
22. Tatone C, Carbone MC, Gallo R, Delle Monache S, Di Cola M, Alesse E, Amicarelli F. Age-associated changes in mouse oocytes during postovulatory in vitro culture: possible role for meiotic kinases and survival factor BCL2. Biol Reprod 2006; 74:395–402.
23. Jessus C, Rime H, Haccard O, Van Lint J, Goris J, Merlevede W, Ozon R. Tyrosine phosphorylation of p34cdc2 and p42 during meiotic maturation of Xenopus oocyte. Antagonistic action of okadaic acid and 6-DMAP. Development 1991; 111:813–820.
24. Ware CB, Barnes FL, Maiki-Laurila M, First NL. Age dependence of bovine oocyte activation. Gamete Res 1989; 22:265–275.
25. Kubiak JZ. Mouse oocytes gradually develop the capacity for activation during the metaphase II arrest. Dev Biol 1989; 136:537–545.
26. Yoshida M, Kijima M, Akita M, Beppu T. Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A. J Biol Chem 1990; 265:17174–17179.
27. Ma W, Zhang D, Hou Y, Li YH, Sun QY, Sun XF, Wang WH. Reduced expression of MAD2, BCL2, and MAP kinase activity in pig oocytes after in vitro aging are associated with defects in sister chromatid segregation during meiosis II and embryo fragmentation after activation. Biol Reprod 2005; 72:373–383.
28. Wang Q, Yin S, Ai JS, Liang CG, Hou Y, Chen DY, Schatten H, Sun QY. Histone deacetylation is required for orderly meiosis. Cell Cycle 2006; 5: 766–774.
29. Turner BM. Histone acetylation and control of gene expression. J Cell Sci 1991; 99(pt 1):13–20.
30. Thorne AW, Kmiciek D, Mitchelson K, Sautiere P, Crane-Robinson C. Patterns of histone acetylation. Eur J Biochem 1990; 193:701–713.
31. Hamatani T, Falco G, Akutsu H, Stagg CA, Sharov AA, Dudekula DB, VanBuren V, Ko MSH. Age-associated alteration of gene expression patterns in mouse oocytes. Hum Mol Genet 2004; 13:2263–2278.
32. Munro J, Barr NI, Ireland H, Morrison V, Parkinson EK. Histone deacetylase inhibitors induce a senescence-like state in human cells by a p16-dependent mechanism that is independent of a mitotic clock. Exp Cell Res 2004; 295:525–538.
33. Ogryzko VV, Hirai TH, Russanova VR, Barbie DA, Howard BH. Human fibroblast commitment to a senescence-like state in response to histone deacetylase inhibitors is cell cycle dependent. Mol Cell Biol 1996; 16: 5210–5218.
34. Place RF, Noonan EJ, Giardina C. HDACs and the senescent phenotype of WI-38 cells. BMC Cell Biol 2005; 6:37.