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Dynamics, regulation and functions

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Histone modifications are associated with many fundamental biological processes in cells. An emerging notion from recent studies is that meiosis stage-dependent histone modifications are crucial for the oocyte development in mammals. In this paper, we review the changes and regulation as well as functions of histone modifications during meiotic maturation of mammalian oocyte, with particular emphasis on histone acetylation, phosphorylation and methylation. In general, dynamic and differential modification patterns have been revealed during oocyte maturation, indicative of functional requirement. Disruption of histone modifications leads to defective chromosome condensation and segregation, delayed maturation progression and even oocyte aging. Although several histone-modifying enzymes have been identified in mammalian oocytes, more works are necessary to determine how they direct histone modifications globally and individually in oocytes. Studies on chromatin modification during oocyte development will have implications for our understanding of the mechanisms controlling nuclear architecture and genomic stability in female germ line.

Introduction

In eukaryotes, the fundamental building component of chromatin is the nucleosome, which is composed of 147 base pairs of DNA and an octamer containing two copies of each of the core histone proteins H2A, H2B, H3 and H4. The histone amino termini exposed on the nucleosome surface is subject to numerous posttranslational modifications including acetylation, phosphorylation, methylation, ADP-ribosylation, ubiquitination, sumoylation, biotinylation and proline isomerization.[1-7] These covalent histone modifications provide an attractive storage mechanism for mitotically- and meiotically inheritable information that can be "read" by various effector proteins. Histone modifications often function in a combinatorial manner to alter chromatin structure and accomplish distinct downstream events. It has been widely accepted that cooperation among histone modifications, both spatial and temporal, is associated with diverse biological functions, such as cell cycle progression, DNA replication and repair, transcriptional activity and chromosome stability.[8-11]

Gamete production is a crucial process in the creation of new life for the next generation. Mammalian oocytes are arrested within ovarian follicles at the diplotene stage of the first meiotic prophase, which is also termed the germinal vesicle (GV) stage. Under stimulation by the pituitary LH surge in vivo or after release from an inhibitory environment, the fully-grown oocytes reinitiate meiosis as indicated by GV breakdown (GVBD).[12] The period between the diplotene stage to the onset of GVBD can be divided into four well-defined stages during porcine oocyte development.[13,14] In GV-I, nuclear membrane and nucleolus are clearly visible and chromatin forms a ring or horseshoe around the nucleolus. In GV-IV, the nuclear membrane is less distinct and the nucleolus disappears completely, and chromatin is seen as an irregular network. These two stages are termed GV and late GV stage (L-GV), respectively, in this review. Just after GVBD, the nuclear membrane entirely vanishes and network-like chromatin is visible, which we call the early GVBD stage (E-GVBD). With further condensation of chromatin, the oocytes progress to pre-metaphase I (Pre-MI) stage. When the microtubules become organized into a bipolar spindle and all chromosomes align at the spindle equator, the oocytes proceed to metaphase I (MI) stage, and subsequently extrude the first polar body, followed by entry into meiosis II and a second arrest at metaphase II (MII) stage.[15,16]

Unlike mitosis, there are many events that specifically occur during meiotic progression, including successive M phases without an intervening DNA replication phase, pairing of homologous chromosomes, and asymmetric cell division, which raises the possibility that particular histone modification patterns may be presented during oocyte maturation and may play meiosis-specific roles. To date, histone modifications during oocyte maturation have been examined in diverse species and substantial results have been reported. In the present review, we focus on the changes, regulation and functions of histone modifications during mammalian oocyte maturation, with a particular emphasis on histone acetylation, methylation and phosphorylation.

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Table 1. Acetylation profiles of various lysine residues on histone H3 and H4 during oocyte maturation

Oocyte		GV	L-GV	E-GVBD	Pre-MI	MI	AI	MII	Refs
Mouse	H3/K9	+			-	-		-	19–23
	H3K14	+			-	-		-	
	H4/K5	+			-	-		-	
	H4/K8	+			±	±		±	
	H4/K12	+			-	-		-	
	H4/K16	+			-	-		-	
Bovine	H4/K5	+			-			-	24
	H4/K8	+			±			±	
	H4/K12	+			-			-	
	H4/K16	+			-			-	
Porcine	H3/K9	+	±	-	+	+	+	+	25–27
	H3K14	+	±	-	+	+	+	+	
	H4/K5	+	±	-	-	-	+	-	
	H4/K8	+	±	-	+	+	+	+	
	H4/K12	+	±	-	+	+	+	+	
	H4/K16	+	±	-	-	-	+	-	
Sheep	H3/K9	+	+		+	±	+	+	28
	H4/K5	-	-		-	±	+	-	
	H4/K12	+	+		+	±	+	+	

Note: Intense and weak fluorescence signals are denoted with + and ±, respectively, and no signal with -. GV, germinal vesicle; L-GV, late GV; E-GVBD, early GV breakdown; Pre-MI, pre-metaphase I; MI, metaphase I; AI, anaphase I; MII, metaphase II.

Table 2. Temporal and spatial distribution of phosphorylated histone H3 during oocyte maturation

Oocyte		GV	L-GV	E-GVBD	Pre-MI	MI	AI	MII	Refs
Mouse	H3/Ser10	+			+/PC	+/PC	+/PC	+	31
	H3/Ser28	-			+/rim	+/rim	+/rim	+/rim	
Porcine	H3/Ser10	-	-	±	+	+	+	+	27, 33
	H3/Ser28	-	-	-	+/rim	+/rim	+/rim	+/rim	

Note: Intense and weak fluorescence signals are denoted with + and ±, respectively, and no signal with -; rim means rim distribution on the chromosomes; PC means intensive distribution in pericentromeric heterochromatin.

Changes in Histone Modifications during Mammalian Oocyte Maturation

Global changes in histone modifications in oocytes at different developmental stages have been examined using a panel of antibodies specific for the acetylated, methylated and phosphorylated forms of histones, mostly by immunofluorescence staining coupled with confocal microscopy. The modification states of histones during mammalian oocyte maturation are summarized in **Tables 1–3**.

Dynamic histone acetylation during mammalian oocyte maturation. All core histones are acetylated in vivo; modifications of histone H3 and H4 are, however, much more extensively characterized than those of H2A and H2B. The critical sites for acetylation include at least four highly conserved lysines (K) in histone H4 (K5, K8, K12, K16) and two in histone H3 (K9, K14).[17,18] The acetylation patterns of histone H3 and H4 during mouse oocyte maturation have been well documented. In general, all examined lysine residues are acetylated (H4/K5ac, H4/K8ac, H4/K12ac, H4/K16ac, H3/K9ac and H3/K14ac) in fully-grown GV oocytes. However, with the resumption of meiosis, the deacetylation takes place in the condensed chromosome and is maintained until MII stage, with the exception of H4/K8ac.[19-23] Bovine oocytes demonstrated a similar acetylation pattern of histone H4 during maturation.[24] Remarkably, the differential acetylation patterns of histones were observed in in vitro-matured porcine oocytes (**Fig. 1**).[25-27] First, the acetylation levels of six lysine residues mentioned above were uniformly decreased at the late GV (L-GV) stage, indicating that histone deacetylation may be required for the orderly progression through GV to GVBD. Second, H4/K5 and H4/K16 were completely deacetylated in MI oocytes, and after transient reacetylation in anaphase I (AI), they were dramatically deacetylated again at MII chromosomes. Interestingly, the intense signals of H4/K5ac and H4/K16ac were still present in the first polar body (**Fig. 1**; arrowheads), indicating that the histone deacetylation of oocytes is regulated by

a meiosis stage-dependent mechanism, and the first polar bodies, which have escaped from the normal cell cycle, are beyond the control of this mechanism. Third, unlike mouse oocytes, the signals of acetylated H4/K8, K12 and H3/K9, 14 can be clearly detected at both MI and MII stages in porcine oocyte, which implies that histone acetylation is not constantly lost in metaphase chromosomes. It should be noted that sheep oocytes showed a unique histone acetylation pattern during meiotic maturation.[28] In sheep oocytes, H3/K9 and H4/K12 were acetylated from GV to GVBD stage, and then deacetylated at MI stage; reacetylation was observed from AI to MII stage. Acetylation of H4/K5 first appeared in MI sheep oocytes and became intensive at AI stage; notably, it was barely detectable at MII chromosomes. Altogether, these findings suggest that histone acetylation is a meiosis stage-dependent and lysine residue-specific process during oocyte maturation, and acetylation patterns are not identical among oocytes from different species.

Temporal and spatial distribution of phosphorylated histone H3 during mammalian oocyte maturation. All core histones contain phosphoacceptor sites in their N-terminal domains: H2A and H4 are phosphorylated on serine 1, H2B on serine 14/32, H3 on serine 10/28 and threonines 3/11.[23,29,30] Among these, the phosphorylation of serine 10 and 28 residue on histone H3 (H3/Ser10ph and H3/Ser28ph) is the most extensively characterized in mammalian oocytes (**Table 2**).

By performing immunostaining on mouse oocytes, we examined the temporal and spatial distribution of phosphorylated H3/Ser10 and H3/Ser28 during porcine oocyte meiotic maturation (**Fig. 2**).[31] At GV stage, staining of H3/Ser28ph was barely observed on chromatin. Upon meiotic resumption, H3/Ser28ph was clearly detectable at the periphery of Pre-MI chromosomes, and this distribution pattern was maintained until MII. We further found that the staining pattern of H3/Ser10ph was completely different from that of H3/Ser28ph in mouse oocytes. The H3/ser10ph staining appears to closely colocalize with the chromatin in GV oocytes. As the oocytes entered into first meiosis, entire chromosomes were covered by the signals of H3/ser10ph, with intensive phosphorylation of H3/Ser10 in pericentromeric heterochromatin at Pre-MI and MI stage (**Fig. 2**; arrowheads). It is interesting to note that the phosphorylation of H3/Ser10 occurred uniformly along the chromosomes in MII oocytes, indicating that H3/Ser10ph might be functionally distinct between metaphase of first and second meiosis. Nevertheless, contradictory results were reported by Swain et al. showing that mouse GV oocytes had no H3/Ser10ph but did have H3Ser28ph;[32] it is not clear why these studies differ.

Distribution and expression of H3/Ser10ph and H3/Ser28ph during porcine oocyte maturation were examined by immunofluorescence and immunoblotting.[27,33] Low expression of phosphorylated H3/Ser10 and 28 were detected in GV oocytes. Following gradual dephosphorylation from GV to L-GV stage, a transient phosphorylation of H3/Ser10 at the periphery of condensed chromatin was reestablished at early GVBD stage (E-GVBD), and then the dramatically increased signals covered whole chromosomes from Pre-MI to MII. By contrast, the presence of H3/Ser28ph rim around meiotic chromosomes persisted from Pre-MI to MII except for the AI stage, which is inconsistent with another report that both H3/Ser10ph and H3/Ser28ph showed similar co-localization with chromatin during porcine oocyte meiosis.[34] Such a discrepancy may be caused by different magnifications used to observe samples. In sum, with oocytes proceed to the

Table 3. Methylation profiles of lysine and arginine residues on histone H3 and H4 during oocyte maturation

Oocyte		GV	Pre-MI	MII	Refs
Mouse	H3/K4me2	+	+	+	23, 38, 42
	H3/K9me2	+	+	+	
	H3/K79me2	+	+	+	
	H3/K79me3	+/PC	+/PC	+/PC	
	H4/R3me2	+		-	
	H3/R17me	+		-	
Porcine	H3/K4me2	+	+	+	39
	H3/K9me2	+	+	+	
	H3/K27me	+		+	
	H3/K27me3	+		+	
Bovine	H3/K9me2	+	+	+	41
Sheep	H3/K9me3	+		+	37
Human	H3/K9me	+	+	+	40
	H4/R3me2	+	+	+	

Note: Intense and no signals are denoted with + and -, respectively; PC means localization in pericentromeric heterochromatin.

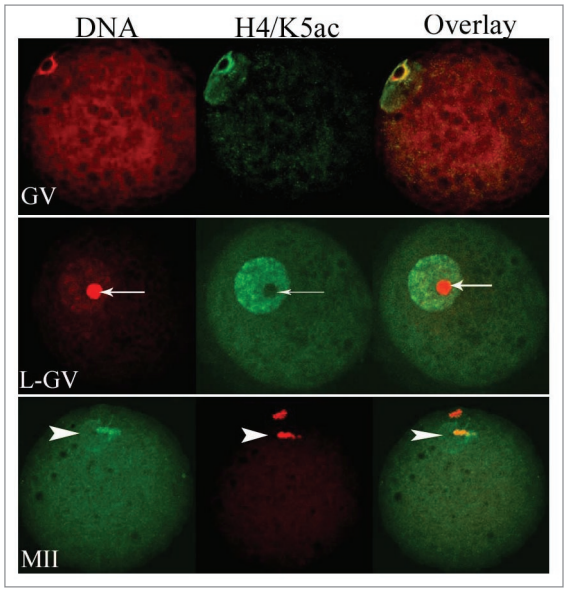

Figure 1. The acetylation patterns of H4/K5 during porcine oocyte maturation. Porcine oocytes at different developmental stages are immunolabeled with antibody against H4/K5ac (green): GV, non-cultured oocytes at germinal vesicle stage; L-GV, oocytes at late germinal vesicle stage, arrowheads indicate the histone deacetylation on the condensed chromatin; MII, oocytes at second metaphase, arrows indicate the acetylation signals in first polar bodies. Each sample is counterstained with PI to visualize DNA (red). From Wang et al. Cell Cycle 2006; 5:766–74 with modifications.

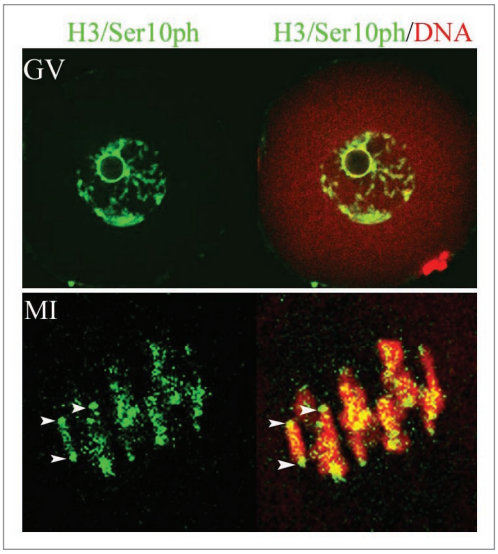

Figure 2. Temporal and spatial distribution of H3/Ser10ph during mouse oocyte maturation. Mouse oocytes at different developmental stages are immunolabeled with antibody against H3/Ser10ph (green): GV, non-cultured oocytes at germinal vesicle stage; MI, oocytes at first metaphase. Arrowheads denote the intensive phosphorylation of H3/Ser10 in pericentromeric heterochromatin. Each sample is counterstained with PI to visualize chromosomes (red). From Wang et al. Cell Cycle 2006; 5:1974–82 with modifications.

Pre-MI stage, the phosphorylation levels of both H3/Ser10 and H3/Ser28 promptly increased; however, the differential distribution patterns exist between them.

Constant histone methylation during mammalian oocyte maturation. The main methylation sites within histone tails are the basic amino acid side chains of lysine (K) and arginine (R) residues. In vivo, methylated lysines can be found either in a mono-, di- or tri-methylated state, whereas arginines can be either mono- or di-methylated.[35,36] So far, the methylation status of different lysine and arginine residues on histone H3 and H4 has been examined in mouse, porcine, sheep, bovine and human oocytes.[20,23,37-42] Immunostaining coupled with confocal microscopy has revealed that, in contrast to acetylation and phosphorylation, histone methylation appears to be relatively stable during oocyte maturation, as shown in **Table 3**. Methylated histones are basically colocalized with chromosomes in mammalian oocytes, whereas H3K79me3 was observed in the pericentromeric heterochromatin regions of meiotic chromosomes.[38] Exceptionally, Sarmento et al. reported the dynamic methylation patterns of H3R17 and H4R3 during mouse oocyte maturation.[23] At GV stage, H3R17me and H4R3me were found throughout the nucleus in a punctate staining pattern and only weakly colocalized with the chromatin. With the completion of meiotic maturation, methylated H3R17 and H4R3 were almost absent from the chromosomes in MII arrested eggs. However, studies in human oocytes showed that H4R3 maintained a constant methylation state during cell cycle progression through GV to MII stage.[40]

Regulation of Histone Modifications in Mammalian Oocyte

Histone acetylation. The steady-state level of histone acetylation is controlled by histone acetyltransferase (HATs) and histone deacetylases (HDACs). More than 17 isoforms of mammalian HDACs have been identified and they are generally classified into three groups: class I (HDACs 1, 2, 3 and 8), class II (HDACs 4, 5, 6, 7, 9 and 10), and class III (SIRTs 1, 2, 3, 4, 5, 6 and 7).[18] The mRNAs of *Hdacs 1, 2, 3, 4, 6, 8, 9* and *Sirt1* are found to be present during mouse oocyte maturation,[43,44] and those of *Hdacs 1, 2, 3* and *7* are present in bovine oocytes.[45]

Immunocytochemical analysis revealed that HDAC1, 2 and 3 were concentrated in the nuclear of fully-grown mouse oocytes. At MI and MII stage, however, only HDAC1 was associated with chromosomes congressed on metaphase plate and this localization correlated with loss of H4/K5 acetylation.[21,46] Surprisingly, our studies in porcine oocytes[26] showed that HDAC1 localized in the chromatin-depleted spaces at GV stage but then translocated to the periphery of condensed chromosomes with the meiotic resumption. Moreover, by performing western blotting on the in vitro-matured porcine oocytes at different developmental stages, we identified that both the phosphorylated and non-phosphorylated HDAC1 isoforms were present during maturation and their expression underwent gradual changes. It has been widely documented that HDAC activity is regulated in multiple ways including protein-protein interaction, posttranslational modification, abundance, as well as by subcellular distribution.[47,48] Above data therefore suggest that subcellular localization, expression level and phosphorylated modification of HDAC1 are likely to co-participate in the regulation of histone acetylation during oocyte maturation.

Real-time quantitative PCR (RT-PCR) analysis showed that HDAC4 transcript was barely detected during oocyte growth, whereas it was readily detectable in fully-grown mouse oocytes. The expression was maintained at a high level until MII stage, and then dramatically decreased after fertilization,[49] indicating that HDAC4 may play specific roles during mouse oocyte maturation. Additionally, HDAC6 has been found to be localized in the cytoplasm of mouse GV oocytes and ectopic expression of this enzyme alters the nuclear structure and causes compaction of the chromatin.[50]

HATs are divided into three families: Gcn5/PCAF (general control of amino-acid synthesis 5/p300-CBP-assocaited factor), p300/CBP (adenoviral E1A-associated protein/CREB-binding protein) and MYST. MYST is an acronym of its four founding memebers: human MOZ (monocytic leukemia zinc finger protein), yeast Ybf2 (renamed Sas3, for something about silencing 3), yeast Sas2, and mammalian TIP60 (HIV Tat-interacting 60 kDa protein).[51-53] High levels of MYST4 mRNA have been found in both GV and MII bovine oocytes. Immunolocalization study showed that MYST4 protein accumulated in the nucleus of GV oocytes, and then concentrated in the vicinity of meiotic spindle rather than on chromosomes when oocytes reached MI stage.[54] Given the global histone deacetylation in metaphase oocytes, it appears unlikely that MYST4 acetylates histone H3

and H4 at this position. The constant expression of HAT1 and Gcn5 mRNA was also detected during bovine oocyte maturation.[45] Identification of HATs and their potential functions in oocytes derived from other mammalian species have not been reported yet.

Akiyama et al. found that roscovitine (an inhibitor of maturation promoting factor, MPF) or cycloheximide (a protein synthesis inhibitor) treatment can prevent H4/K12 deacetylation during both the first and second meiosis in mouse oocyte, leading the authors to conclude that p34cdc2 kinase activity is essential for H4/K12 deacetylation and the deacetylated state is maintained by newly synthesized proteins that inhibits HATs activity in meiosis.[19] However, by conducting the artificial GV destruction (AGVD), Endo et al. demonstrated that the MPF and MAPK activities were dispensable for the deacetylation of H3/K9 and H4/K12 in porcine oocytes.[55] Furthermore, they revealed that nuclear contents, including class I HDACs, are not required for the global histone deacetylation during oocyte maturation, and that cytoplasmic HDACs other than class I are responsible for this process.[56] Further study of the expression and function of various HDACs and HATs should provide important clues for uncovering the mechanism by which histone acetylation is involved in regulating meiotic maturation.

Histone phosphorylation. Although H3/Ser10 can be phosphorylated by multiple kinases under different conditions,[57-59] Aurora B is the most important kinase that phosphorylates this residue in vivo during mitosis and meiosis.[60-63] Aurora B is also known to phosphorylate Ser28 of histone H3 in mitotic cells.[64,65] Recently, Jelinkova et al. showed that activation of Aurora B preceded phosphorylation of H3/Ser10 during porcine oocyte maturation, and ZM447439 (an inhibitor of Aurora kinase family) treatment prevented the Aurora B activity and the phosphorylation of H3/Ser10, but not the phosphorylation of H3/Ser28.[34] Interestingly, we found that inhibition of Aurora kinase significantly decreased the phosphorylation levels of both H3/Ser10 and H3/Ser28 in mouse oocyte, resulting in chromosome misalignment.[31] These observations suggest that Aurora kinase participates in the regulation of histone H3 phosphorylation during oocyte meiosis, which may be essential for the correct chromosome alignment and segregation. On the other hand, the phosphatase that dephosphorylates H3/Ser10 has been identified as protein phosphasetase 1 (PP1) in budding yeast and nematodes.[61,66] Treatment of immature porcine oocytes with okadaic acid (OA) and calyculin A (CL-A), the PP1/PP2a inhibitors, induced rapid chromosome condensation with hyperphosphorylated histone H3.[67] Similarly, mouse oocytes treated with OA displayed increased phosphorylation of histone H3 at both Ser10 and Ser28 compared to controls.[32] Given these findings, it is possible that a balance of Aurora B kinase and PP1/PP2A activities regulates the meiotic phosphorylation of histone H3 in mammalian oocytes.

Histone methylation. Histone lysine methylation is catalyzed by a family of proteins that contain a SET domain and by yeast Dot1 and its mammalian homologue, DOT1L, which use a novel enzymatic domain.[36] The methylation status of H3/K9 is associated with the activity of the histone methyltransferases (HMTs) HLA-B-associated transcript 8 (G9A) and suppressor of variegation 3-9 homolog 1 (SUV39H1).[68] RT-PCR revealed that the mRNA levels of G9A and SUV39H1 were significantly increased during bovine oocyte growth.[41] Remarkably, accompanying with meiotic maturation, the relative abundance of SUV39H1 dramatically decreased in mouse and bovine oocyte.[69,70] G9A transcripts were absent in immature and matured mouse oocytes[70] and downregulated in bovine oocytes.[41,69] PcG proteins enhancer of zeste2 (EZH2) is one of HMTs responsible for methylating H3/K27.[71] Park et al. found that the expression of EZH2 mRNA slightly reduced during porcine oocyte maturation.[39] Although these HMTs experience the fluctuations in mRNA expression during oocyte maturation, the methylation status of H3/K9 and H3/K27 appears not to be affected.[39,41] In addition, elimination of methylated arginine 3 residues of histone H4 (H4/R3) is catalyzed by the peptidyl arginine deimidase (PAD) enzyme in several human cell lines.[72,73] PAD is expressed in mouse oocytes, where it has been suggested to play a role in the removal of methylated H4/R3 from condensing chromosomes after the resumption of meiosis.[23,74]

Collectively, although several enzymes catalyze histone modifications have been identified in mammalian oocytes, data regarding transcript and protein abundance is insufficient to draw a mechanistic conclusion with regard to how these enzymes modify oocyte histones globally and individually.

Functions of Histone Modifications during Mammalian Oocyte Maturation

The dynamic nature of histone modifications during mammalian oocyte maturation indicates that they may play meiosis-specific roles. Several critical events in oocyte meiosis have been reported to be influenced by histone modifications; the following sections will give a brief summary.

Histone modifications and chromosome organization. Chromosome condensation is the first visible process occurring at the beginning of oocyte maturation, which is essential for the correct packaging of chromatin fibers into chromosomes and subsequent fidelity of chromosome segregation into daughter cells. In mammalian oocytes at the growing diplotene stage, the chromosomes are found in a decondensed arrangement called nonsurrounded nucleolus (NSN). Subsequently, the chromosomes condense into a ring around the nucleolus and also a threadlike pattern in the rest nuclear space, which is called surrounded nucleolus (SN). The transition from NSN to SN configuration is critical for the acquisition of full developmental competence for the oocyte.[75] Quantification of immunofluorescence signals revealed that the levels of H4/K5 and H4/K12 acetylation, and H3/K9 methylation were higher in SN-type mouse oocytes than in NSN-type oocytes.[20] Inhibition of HDACs activity with trichostatin A (TSA, a general inhibitor of HDACs) in pre-ovulatory oocytes that exhibit the SN configuration resulted in a striking decondensation of euchromatin regions.[76] Moreover, our confocal microscopy analysis showed that distinct lysines on histone H3 and H4 exhibit a uniform deacetylation tendency with gradual chromatin condensation through GV to late GV stage during

porcine oocyte meiosis. Importantly, such chromatin condensation could be disrupted by TSA treatment, showing chromatin clumps or strands around the nucleolus.[26] These findings indicate the potential connection between histone (de)acetylation and chromatin organization during oocyte growth. In addition, many works have shown that multiple components of chromatin, especially histone modifications, are involved in the Heterochromatin protein 1 (HP1) binding to certain sites of genome.[77,78] We found that HP1α always colocalized with H4/K5ac, H3/K4me2 and H3/Ser10ph in immature mouse oocytes. Furthermore, dynamic migration of HP1α was observed in germinal vesicle with NSN to SN oocytes, indicative of its involvement in the transition of chromatin configuration.[42] Therefore, it is possible that histone modifications may influence chromatin remodeling in mammalian oocytes by regulating HP1 dynamics.

Numerous data suggest that there is a strong correlation between the phosphorylation of H3/Ser10 and chromosome condensation in mitotic cells.[79-82] Nonetheless, contradictory conclusions about the relationship between histone H3 phosphorylation and chromosome condensation were obtained in oocytes. Bui et al. reported that the changes in histone H3 kinase activity accurately correspond with the phosphorylation of H3/Ser10 and chromosome condensation during porcine oocyte maturation, implicating that H3/Ser10ph is a key event in meiotic chromosome condensation.[27,67] In contrast, by setting up a model using oocytes cultured with inhibitors of proteosynthesis cyclin-dependent kinases, or specifically Aurora kinase, Jelinkova et al. demonstrated that neither Aurora kinase activity nor histone H3 phosphorylation is required for chromosome condensation in porcine oocytes and that these changes are rather concomitant events, which might be important for further processing of chromosome during later stages of meiosis.[34] In support of this idea, we did not observe apparent coupling between the phosphorylation of H3/Ser10 and chromosome condensation in mouse oocytes and early embryos.[31]

Additionally, we found that the phsophorylation of H3/Ser28 is punctually triggered in Pre-MI oocytes and prophase embryos.[31,33] Similar results were reported in mitotic cells, showing that H3/Ser28ph always initiated in condensed chromosomes at prophase.[64,83,84] Thus, phosphorylation of H3/Ser28 might be a critical factor associated with chromosome condensation. Other less-well-understood candidates that may indeed be the phosphorylation relevant to condensation include H2ASer1ph, H2BSer10ph, H2ATur119ph and H4ph.[85-88]

Histone modifications and chromosome segregation. Histone acetylation has been reported to be associated with chromosome segregation in oocyte meiosis. Treatment with TSA induces histone hyperacetylation and a high frequency of spindle defects and chromosome missegregation in mouse and porcine oocytes.[26,89] Furthermore, failure to deacetylate histones in meiosis has been demonstrated to result in aneuploidy in mouse eggs.[90] Accurate segregation of homologous chromosomes or sister chromatids during anaphase is a critical event in meiosis or mitosis. Any error in this process may result in early embryo death, spontaneous abortion and genetic diseases.[90,91] Chromosome movement depends on the establishment of physical and biochemical interactions between spindle microtubules and specialized chromosomal regions localized at centromeric heterochromatin.[92] The centromeric chromatin with particular histone modification is essential for the formation of a functional kinetochore. Considerable evidence suggests that underacetylated state of histones in centromeric chromatin is required for the recruitment of specific heterochromatin protein in mitosis.[93,94] Studies in mouse oocytes also indicate that pharmacological inhibition of HDACs during meiotic progression disrupted the binding of ATRX, a member of the SNF2 family of helicase/ATPases, to centromeric domains.[89] Based on these findings, it is reasonable to propose that histone hyperacetylation may disrupt the centromeric heterochromatin domain, as a result, weakened interactions between kinetochores and spindle microtubules are established, causing the deficient chromosome segregation in oocyte meiosis.[26,89,93] On the other hand, by performing confocal scanning, we identified the intensive phosphorylation of H3/Ser10 at pericentromeric heterochromatin in metaphase/anaphase mouse oocytes. Importantly, TSA treatment significantly resulted in the dephosphorylation of histone H3/Ser10 in this region.[31] Similarly, addition of histone deacetylase inhibitors prior to the end of S-phase resulted in a decrease of phosphorylation at pericentromeric histone H3 in G_2 phase in two human tumor cell lines.[95] These data suggest that dephosphorylation of H3/Ser10 may be responsible, at least in part, for TSA-induced defective chromosome segregation. Abnormal chromosome segregation was also observed in a Tetrahymena mutant strain produced by replacing serine 10 of histone H3 with alanine.[96] Altogether we conclude that H3/Ser10 phosphorylation in pericentromeric heterochromatin may participate in the regulation of chromosome segregation during oocyte meiosis.

Histone acetylation and meiotic progression. Upon meiotic resumption, dramatic changes in histone acetylation are observed in oocytes, indicative of functional requirements during these stages. Generally, the acetylation states of all examined lysine residues were uniformly and dramatically reduced from GV stage to GVBD stage in mammalian oocytes (**Table 1**). By preventing histone deacetylation with TSA during this course, we found that the onset of GVBD was markedly delayed in porcine oocytes. Similarly, it has been reported that incubation of mammalian cell lines with inhibitors of HDACs induces an arrest in G_1 or G_2/M phase.[97,98] Simultaneous substitution of four conserved lysine residues in histone H4 by glutamine activates the G_2/M checkpoint and introduction of a single acetylatable lysine in the mutant histone tail suppresses the G_2/M cell cycle defects in *y*east.[99,100] These findings indicate that disruption of histone acetylation status may result in improper chromosome condensation, which further affects kinetochore-microtubule interaction and induces checkpoint activation, causing cell cycle arrest in the G_2 phase.

We did not observe any apparent effects of histone hyperacetylation induced by TSA on progression through Pre-MI to MII in porcine oocytes,[26] which is consistent with the Aoki lab's finding in mouse oocytes.[21,90] Nevertheless, De La Fuente et al.[89] found that exposure to TSA during meiotic maturation resulted in significant proportion of mouse oocyte that remained at MI

stage. This discrepancy in the effects of TSA treatment on meiotic maturation remains to be elucidated.

Histone acetylation and oocyte aging. Oocytes arrested at MII stage are normally fertilized soon after ovulation. If fertilization does not occur within a optimal window, unfertilized oocytes remaining in the oviduct (in vivo aging) or culture (in vitro aging) will undergo a time-dependent deterioration in quality, a process called "oocyte aging."[101] The acetylation state of histones has been compared between oocytes from younger and older mice by immunostaining. Remarkably, the acetylation levels of H3/K14, H4/K8 and H4/K12 were gradually increased during in vivo and in vitro postovulatory aging,[90,102,103] suggesting a deficiency in the mechanism regulating histone deacetylation in the aged oocytes. Moreover, TSA treatment-induced histone hyperacetylation can accelerate the progression of postovulatory aging, leading to the decreased rate of fertilization and subsequent embryonic development.[102,103] Interestingly, in vitro culture experiment has demonstrated that caffeine treatment can block the histone acetylation during oocyte aging.[102] Regardless, the pathway(s) by which histone acetylation affects oocyte aging remains unclear.

Concluding Remarks

In conclusion, spatial and temporal expression of histone acetylation, methylation and phosphorylation has been extensively examined during mammalian oocyte maturation. These histone modifications are involved in multiple meiotic events in oocytes. Nevertheless, the contribution of individual modification (like just H4/K5ac) is difficult to discern at present due to lack of tools to ablate each of them. More works are necessary to identify and determine the substrate specificity of the enzymes that regulate histone modifications in mammalian oocyte. Furthermore, the information on other types of modifications, such as sumoylation, biotinylation, ADP ribosylation, proline isomerization and deimination, is rather limited and a direct association of these modifications with mammalian oocyte development remains to be explored. Studies on histone modifications in chromatin during mammalian oocyte development will have wide-ranging implications for our understanding of the mechanisms controlling nuclear architecture and genomic stability in female germ line.

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References

1. Allfrey VG, Faulkner R, Mirsky AE. Acetylation and methylation of histones and their possible role in the regulation of rna synthesis. Proc Natl Acad Sci USA 1964; 51:786-94.
2. Gutierrez RM, Hnilica LS. Tissue specificity of histone phosphorylation. Science 1967; 157:1324-5.
3. Huletsky A, Niedergang C, Frechette A, Aubin R, Gaudreau A, Poirier GG. Sequential ADP-ribosylation pattern of nucleosomal histones. ADP-ribosylation of nucleosomal histones. Eur J Biochem 1985; 146:277-85.
4. Nathan D, Ingvarsdottir K, Sterner DE, Bylebyl GR, Dokmanovic M, Dorsey JA, et al. Histone sumoylation is a negative regulator in *Saccharomyces cerevisiae* and shows dynamic interplay with positive-acting histone modifications. Genes Dev 2006; 20:966-76.
5. Xu D, Bai J, Duan Q, Costa M, Dai W. Covalent modifications of histones during mitosis and meiosis. Cell Cycle 2009; 8:3688-94.
6. Rada-Iglesias A, Enroth S, Andersson R, Wanders A, Pahlman L, Komorowski J, et al. Histone H3 lysine 27 trimethylation in adult differentiated colon associated to cancer DNA hypermethylation. Epigenetics 2009; 4:107-13.
7. Koprinarova MA, Russev GC. Dynamics of histone H4 acetylation during the cell cycle. Cell Cycle 2008; 7:414-6.
8. Kouzarides T. Chromatin modifications and their function. Cell 2007; 128:693-705.
9. Strahl BD, Allis CD. The language of covalent histone modifications. Nature 2000; 403:41-5.
10. Bloushtain-Qimron N, Yao J, Shipitsin M, Maruyama R, Polyak K. Epigenetic patterns of embryonic and adult stem cells. Cell Cycle 2009; 8:809-17.
11. Wang N, Tilly JL. Epigenetic status determines germ cell meiotic commitment in embryonic and postnatal mammalian gonads. Cell Cycle 9:339-49.
12. Fan HY, Sun QY. Involvement of mitogen-activated protein kinase cascade during oocyte maturation and fertilization in mammals. Biol Reprod 2004; 70:535-47.
13. Motlik J, Fulka J. Breakdown of the germinal vesicle in pig oocytes in vivo and in vitro. J Exp Zool 1976; 198:155-62.
14. Sun XS, Liu Y, Yue KZ, Ma SF, Tan JH. Changes in germinal vesicle (GV) chromatin configurations during growth and maturation of porcine oocytes. Mol Reprod Dev 2004; 69:228-34.
15. Wang Q, Sun QY. Evaluation of oocyte quality: morphological, cellular and molecular predictors. Reprod Fertil Dev 2007; 19:1-12.
16. Sun QY, Miao YL, Schatten H. Towards a new understanding on the regulation of mammalian oocyte meiosis resumption. Cell Cycle 2009; 8:2741-7.
17. Bjerling P, Silverstein RA, Thon G, Caudy A, Grewal S, Ekwall K. Functional divergence between histone deacetylases in fission yeast by distinct cellular localization and in vivo specificity. Mol Cell Biol 2002; 22:2170-81.
18. de Ruijter AJ, van Gennip AH, Caron HN, Kemp S, van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J 2003; 370:737-49.
19. Akiyama T, Kim JM, Nagata M, Aoki F. Regulation of histone acetylation during meiotic maturation in mouse oocytes. Mol Reprod Dev 2004; 69:222-7.
20. Kageyama S, Liu H, Kaneko N, Ooga M, Nagata M, Aoki F. Alterations in epigenetic modifications during oocyte growth in mice. Reproduction 2007; 133:85-94.
21. 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.
22. Nagashima T, Maruyama T, Furuya M, Kajitani T, Uchida H, Masuda H, et al. Histone acetylation and subcellular localization of chromosomal protein BRD4 during mouse oocyte meiosis and mitosis. Mol Hum Reprod 2007; 13:141-8.
23. Sarmento OF, Digilio LC, Wang Y, Perlin J, Herr JC, Allis CD, et al. Dynamic alterations of specific histone modifications during early murine development. J Cell Sci 2004; 117:4449-59.
24. Maalouf WE, Alberio R, Campbell KH. Differential acetylation of histone H4 lysine during development of in vitro fertilized, cloned and parthenogenetically activated bovine embryos. Epigenetics 2008; 3:199-209.
25. Endo T, Naito K, Aoki F, Kume S, Tojo H. Changes in histone modifications during in vitro maturation of porcine oocytes. Mol Reprod Dev 2005; 71:123-8.
26. Wang Q, Yin S, Ai JS, Liang CG, Hou Y, Chen DY, et al. Histone deacetylation is required for orderly meiosis. Cell Cycle 2006; 5:766-74.
27. Bui HT, Van Thuan N, Kishigami S, Wakayama S, Hikichi T, Ohta H, et al. Regulation of chromatin and chromosome morphology by histone H3 modifications in pig oocytes. Reproduction 2007; 133:371-82.
28. Tang LS, Wang Q, Xiong B, Hou Y, Zhang YZ, Sun QY, et al. Dynamic changes in histone acetylation during sheep oocyte maturation. J Reprod Dev 2007; 53:555-61.
29. Polioudaki H, Markaki Y, Kourmouli N, Dialynas G, Theodoropoulos PA, Singh PB, et al. Mitotic phosphorylation of histone H3 at threonine 3. FEBS Lett 2004; 560:39-44.
30. Preuss U, Landsberg G, Scheidtmann KH. Novel mitosis-specific phosphorylation of histone H3 at Thr11 mediated by Dlk/ZIP kinase. Nucleic Acids Res 2003; 31:878-85.
31. Wang Q, Wang CM, Ai JS, Xiong B, Yin S, Hou Y, et al. Histone phosphorylation and pericentromeric histone modifications in oocyte meiosis. Cell Cycle 2006; 5:1974-82.
32. Swain JE, Ding J, Brautigan DL, Villa-Moruzzi E, Smith GD. Proper chromatin condensation and maintenance of histone H3 phosphorylation during mouse oocyte meiosis requires protein phosphatase activity. Biol Reprod 2007; 76:628-38.

33. Gu L, Wang Q, Wang CM, Hong Y, Sun SG, Yang SY, et al. Distribution and expression of phosphorylated histone H3 during porcine oocyte maturation. Mol Reprod Dev 2008; 75:143-9.
34. Jelinkova L, Kubelka M. Neither Aurora B activity nor histone H3 phosphorylation is essential for chromosome condensation during meiotic maturation of porcine oocytes. Biol Reprod 2006; 74:905-12.
35. Bannister AJ, Schneider R, Kouzarides T. Histone methylation: dynamic or static? Cell 2002; 109:801-6.
36. Klose RJ, Zhang Y. Regulation of histone methylation by demethylimination and demethylation. Nat Rev Mol Cell Biol 2007; 8:307-18.
37. Hou J, Liu L, Zhang J, Cui XH, Yan FX, Guan H, et al. Epigenetic modification of histone 3 at lysine 9 in sheep zygotes and its relationship with DNA methylation. BMC Dev Biol 2008; 8:60.
38. Ooga M, Inoue A, Kageyama S, Akiyama T, Nagata M, Aoki F. Changes in H3K79 methylation during preimplantation development in mice. Biol Reprod 2008; 78:413-24.
39. Park KE, Magnani L, Cabot RA. Differential remodeling of mono- and trimethylated H3K27 during porcine embryo development. Mol Reprod Dev 2009; 76:1033-42.
40. Qiao J, Chen Y, Yan LY, Yan J, Liu P, Sun QY. Changes in histone methylation during human oocyte maturation and IVF- or ICSI-derived embryo development. Fertil Steril 2009. 93:1628-36.
41. Racedo SE, Wrenzycki C, Lepikhov K, Salamone D, Walter J, Niemann H. Epigenetic modifications and related mRNA expression during bovine oocyte in vitro maturation. Reprod Fertil Dev 2009; 21:738-48.
42. Wang Q, Ai JS, Idowu Ola S, Gu L, Zhang YZ, Chen DY, et al. The spatial relationship between heterochromatin protein 1alpha and histone modifications during mouse oocyte meiosis. Cell Cycle 2008; 7:513-20.
43. Pan H, O'Brien MJ, Wigglesworth K, Eppig JJ, Schultz RM. Transcript profiling during mouse oocyte development and the effect of gonadotropin priming and development in vitro. Dev Biol 2005; 286:493-506.
44. Yoshida N, Brahmajosyula M, Shoji S, Amanai M, Perry AC. Epigenetic discrimination by mouse metaphase II oocytes mediates asymmetric chromatin remodeling independently of meiotic exit. Dev Biol 2007; 301:464-77.
45. McGraw S, Robert C, Massicotte L, Sirard MA. Quantification of histone acetyltransferase and histone deacetylase transcripts during early bovine embryo development. Biol Reprod 2003; 68:383-9.
46. Ma P, Schultz RM. Histone deacetylase 1 (HDAC1) regulates histone acetylation, development, and gene expression in preimplantation mouse embryos. Dev Biol 2008; 319:110-20.
47. Sengupta N, Seto E. Regulation of histone deacetylase activities. J Cell Biochem 2004; 93:57-67.
48. Smillie DA, Llinas AJ, Ryan JT, Kemp GD, Sommerville J. Nuclear import and activity of histone deacetylase in Xenopus oocytes is regulated by phosphorylation. J Cell Sci 2004; 117:1857-66.
49. Kageyama S, Liu H, Nagata M, Aoki F. Stage specific expression of histone deacetylase 4 (HDAC4) during oogenesis and early preimplantation development in mice. J Reprod Dev 2006; 52:99-106.
50. Verdel A, Seigneurin-Berny D, Faure AK, Eddahbi M, Khochbin S, Nonchev S. HDAC6-induced premature chromatin compaction in mouse oocytes and fertilised eggs. Zygote 2003; 11:323-8.
51. Carrozza MJ, Utley RT, Workman JL, Cote J. The diverse functions of histone acetyltransferase complexes. Trends Genet 2003; 19:321-9.
52. Yang XJ. The diverse superfamily of lysine acetyltransferases and their roles in leukemia and other diseases. Nucleic Acids Res 2004; 32:959-76.
53. Thomas T, Voss AK. The diverse biological roles of MYST histone acetyltransferase family proteins. Cell Cycle 2007; 6:696-704.
54. McGraw S, Morin G, Vigneault C, Leclerc P, Sirard MA. Investigation of MYST4 histone acetyltransferase and its involvement in mammalian gametogenesis. BMC Dev Biol 2007; 7:123.
55. Endo T, Naito K, Kume S, Nishimura Y, Kashima K, Tojo H. Activities of maturation-promoting factor (MPF) and mitogen-activated protein kinase (MAPK) are not required for the global histone deacetylation observed after germinal vesicle breakdown (GVBD) in porcine oocytes. Reproduction 2006; 131:439-47.
56. Endo T, Kano K, Naito K. Nuclear histone deacetylases are not required for global histone deacetylation during meiotic maturation in porcine oocytes. Biol Reprod 2008; 78:1073-80.
57. He Z, Cho YY, Ma WY, Choi HS, Bode AM, Dong Z. Regulation of ultraviolet B-induced phosphorylation of histone H3 at serine 10 by Fyn kinase. J Biol Chem 2005; 280:2446-54.
58. Schmitt A, Gutierrez GJ, Lenart P, Ellenberg J, Nebreda AR. Histone H3 phosphorylation during Xenopus oocyte maturation: regulation by the MAP kinase/p90Rsk pathway and uncoupling from DNA condensation. FEBS Lett 2002; 518:23-8.
59. Hans F, Dimitrov S. Histone H3 phosphorylation and cell division. Oncogene 2001; 20:3021-7.
60. Giet R, Glover DM. Drosophila aurora B kinase is required for histone H3 phosphorylation and condensin recruitment during chromosome condensation and to organize the central spindle during cytokinesis. J Cell Biol 2001; 152:669-82.
61. Hsu JY, Sun ZW, Li X, Reuben M, Tatchell K, Bishop DK, et al. Mitotic phosphorylation of histone H3 is governed by Ipl1/aurora kinase and Glc7/PP1 phosphatase in budding yeast and nematodes. Cell 2000; 102:279-91.
62. Crosio C, Fimia GM, Loury R, Kimura M, Okano Y, Zhou H, et al. Mitotic phosphorylation of histone H3: spatio-temporal regulation by mammalian Aurora kinases. Mol Cell Biol 2002; 22:874-85.
63. George O, Johnston MA, Shuster CB. Aurora B kinase maintains chromatin organization during the MI to MII transition in surf clam oocytes. Cell Cycle 2006; 5:2648-56.
64. Goto H, Yasui Y, Nigg EA, Inagaki M. Aurora-B phosphorylates Histone H3 at serine28 with regard to the mitotic chromosome condensation. Genes Cells 2002; 7:11-7.
65. Sugiyama K, Sugiura K, Hara T, Sugimoto K, Shima H, Honda K, et al. Aurora-B associated protein phosphatases as negative regulators of kinase activation. Oncogene 2002; 21:3103-11.
66. Francisco L, Wang W, Chan CS. Type 1 protein phosphatase acts in opposition to IpL1 protein kinase in regulating yeast chromosome segregation. Mol Cell Biol 1994; 14:4731-40.
67. Bui HT, Yamaoka E, Miyano T. Involvement of histone H3 (Ser10) phosphorylation in chromosome condensation without Cdc2 kinase and mitogen-activated protein kinase activation in pig oocytes. Biol Reprod 2004; 70:1843-51.
68. Smith CM, Haimberger ZW, Johnson CO, Wolf AJ, Gafken PR, Zhang Z, et al. Heritable chromatin structure: mapping "memory" in histones H3 and H4. Proc Natl Acad Sci USA 2002; 99:16454-61.
69. Nowak-Imialek M, Wrenzycki C, Herrmann D, Lucas-Hahn A, Lagutina I, Lemme E, et al. Messenger RNA expression patterns of histone-associated genes in bovine preimplantation embryos derived from different origins. Mol Reprod Dev 2008; 75:731-43.
70. Oliveri RS, Kalisz M, Schjerling CK, Andersen CY, Borup R, Byskov AG. Evaluation in mammalian oocytes of gene transcripts linked to epigenetic reprogramming. Reproduction 2007; 134:549-58.
71. Czermin B, Melfi R, McCabe D, Seitz V, Imhof A, Pirrotta V. Drosophila enhancer of Zeste/ESC complexes have a histone H3 methyltransferase activity that marks chromosomal Polycomb sites. Cell 2002; 111:185-96.
72. Cuthbert GL, Daujat S, Snowden AW, Erdjument-Bromage H, Hagiwara T, Yamada M, et al. Histone deimination antagonizes arginine methylation. Cell 2004; 118:545-53.
73. Wang Y, Wysocka J, Sayegh J, Lee YH, Perlin JR, Leonelli L, et al. Human PAD4 regulates histone arginine methylation levels via demethylimination. Science 2004; 306:279-83.
74. Wright PW, Bolling LC, Calvert ME, Sarmento OF, Berkeley EV, Shea MC, et al. ePAD, an oocyte and early embryo-abundant peptidylarginine deiminase-like protein that localizes to egg cytoplasmic sheets. Dev Biol 2003; 256:73-88.
75. Zuccotti M, Garagna S, Merico V, Monti M, Alberto Redi C. Chromatin organisation and nuclear architecture in growing mouse oocytes. Mol Cell Endocrinol 2005; 234:11-7.
76. De La Fuente R. Chromatin modifications in the germinal vesicle (GV) of mammalian oocytes. Dev Biol 2006; 292:1-12.
77. Fischle W, Tseng BS, Dormann HL, Ueberheide BM, Garcia BA, Shabanowitz J, et al. Regulation of HP1-chromatin binding by histone H3 methylation and phosphorylation. Nature 2005; 438:1116-22.
78. Stewart MD, Li J, Wong J. Relationship between histone H3 lysine 9 methylation, transcription repression and heterochromatin protein 1 recruitment. Mol Cell Biol 2005; 25:2525-38.
79. Hendzel MJ, Wei Y, Mancini MA, Van Hooser A, Ranalli T, Brinkley BR, et al. Mitosis-specific phosphorylation of histone H3 initiates primarily within pericentromeric heterochromatin during G_2 and spreads in an ordered fashion coincident with mitotic chromosome condensation. Chromosoma 1997; 106:348-60.
80. Van Hooser A, Goodrich DW, Allis CD, Brinkley BR, Mancini MA. Histone H3 phosphorylation is required for the initiation, but not maintenance, of mammalian chromosome condensation. J Cell Sci 1998; 111:3497-506.
81. Wei Y, Mizzen CA, Cook RG, Gorovsky MA, Allis CD. Phosphorylation of histone H3 at serine 10 is correlated with chromosome condensation during mitosis and meiosis in Tetrahymena. Proc Natl Acad Sci USA 1998; 95:7480-4.
82. Houben A, Wako T, Furushima-Shimogawara R, Presting G, Kunzel G, Schubert II, et al. Short communication: the cell cycle dependent phosphorylation of histone H3 is correlated with the condensation of plant mitotic chromosomes. Plant J 1999; 18:675-9.
83. Gernand D, Demidov D, Houben A. The temporal and spatial pattern of histone H3 phosphorylation at serine 28 and serine 10 is similar in plants but differs between mono- and polycentric chromosomes. Cytogenet Genome Res 2003; 101:172-6.
84. Goto H, Tomono Y, Ajiro K, Kosako H, Fujita M, Sakurai M, et al. Identification of a novel phosphorylation site on histone H3 coupled with mitotic chromosome condensation. J Biol Chem 1999; 274:25543-9.
85. Ahn SH, Henderson KA, Keeney S, Allis CD. H2B (Ser10) phosphorylation is induced during apoptosis and meiosis in *S. cerevisiae*. Cell Cycle 2005; 4:780-3.
86. Barber CM, Turner FB, Wang Y, Hagstrom K, Taverna SD, Mollah S, et al. The enhancement of histone H4 and H2A serine 1 phosphorylation during mitosis and S-phase is evolutionarily conserved. Chromosoma 2004; 112:360-71.
87. Ivanovska I, Khandan T, Ito T, Orr-Weaver TL. A histone code in meiosis: the histone kinase, NHK-1, is required for proper chromosomal architecture in Drosophila oocytes. Genes Dev 2005; 19:2571-82.
88. Ivanovska I, Orr-Weaver TL. Histone modifications and the chromatin scaffold for meiotic chromosome architecture. Cell Cycle 2006; 5:2064-71.
89. De La Fuente R, Viveiros MM, Wigglesworth K, Eppig JJ. ATRX, a member of the SNF2 family of helicase/ATPases, is required for chromosome alignment and meiotic spindle organization in metaphase II stage mouse oocytes. Dev Biol 2004; 272:1-14.

90. Akiyama T, Nagata M, Aoki F. Inadequate histone deacetylation during oocyte meiosis causes aneuploidy and embryo death in mice. Proc Natl Acad Sci USA 2006; 103:7339-44.
91. Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet 2001; 2:280-91.
92. Carroll CW, Straight AF. Centromere formation: from epigenetics to self-assembly. Trends Cell Biol 2006; 16:70-8.
93. Ekwall K, Olsson T, Turner BM, Cranston G, Allshire RC. Transient inhibition of histone deacetylation alters the structural and functional imprint at fission yeast centromeres. Cell 1997; 91:1021-32.
94. Taddei A, Maison C, Roche D, Almouzni G. Reversible disruption of pericentric heterochromatin and centromere function by inhibiting deacetylases. Nat Cell Biol 2001; 3:114-20.
95. Robbins AR, Jablonski SA, Yen TJ, Yoda K, Robey R, Bates SE, et al. Inhibitors of histone deacetylases alter kinetochore assembly by disrupting pericentromeric heterochromatin. Cell Cycle 2005; 4:717-26.
96. Wei Y, Yu L, Bowen J, Gorovsky MA, Allis CD. Phosphorylation of histone H3 is required for proper chromosome condensation and segregation. Cell 1999; 97:99-109.
97. Toth KF, Knoch TA, Wachsmuth M, Frank-Stohr M, Stohr M, Bacher CP, et al. Trichostatin A-induced histone acetylation causes decondensation of interphase chromatin. J Cell Sci 2004; 117:4277-87.
98. Yamashita Y, Shimada M, Harimoto N, Rikimaru T, Shirabe K, Tanaka S, et al. Histone deacetylase inhibitor trichostatin A induces cell cycle arrest/apoptosis and hepatocyte differentiation in human hepatoma cells. Int J Cancer 2003; 103:572-6.
99. Bird AW, Yu DY, Pray-Grant MG, Qiu Q, Harmon KE, Megee PC, et al. Acetylation of histone H4 by Esa1 is required for DNA double-strand break repair. Nature 2002; 419:411-5.
100. Megee PC, Morgan BA, Smith MM. Histone H4 and the maintenance of genome integrity. Genes Dev 1995; 9:1716-27.
101. Miao YL, Kikuchi K, Sun QY, Schatten H. Oocyte aging: cellular and molecular changes, developmental potential and reversal possibility. Hum Reprod Update 2009; 15:573-85.
102. Huang JC, Yan LY, Lei ZL, Miao YL, Shi LH, Yang JW, et al. Changes in histone acetylation during postovulatory aging of mouse oocyte. Biol Reprod 2007; 77:666-70.
103. Suo L, Meng QG, Pei Y, Yan CL, Fu XW, Bunch TD, et al. Changes in acetylation on lysine 12 of histone H4 (acH4K12) of murine oocytes during maternal aging may affect fertilization and subsequent embryo development. Fertil Steril 2010; 93:945-51.