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Review

Chromatin modifications in the germinal vesicle (GV) of mammalian oocytes

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Abstract

The nucleus of eukaryotic cells is organized into functionally specialized compartments that are essential for the control of gene expression, chromosome architecture and cellular differentiation. The mouse oocyte nucleus or germinal vesicle (GV) exhibits a unique chromatin configuration that is subject to dynamic modifications during oogenesis. This process of 'epigenetic maturation' is critical to confer the female gamete with meiotic as well as developmental competence. In spite of its biological significance, little is known concerning the cellular and molecular mechanisms regulating large-scale chromatin structure in mammalian oocytes. Here, recent findings that provide mechanistic insight into the complex relationship between large-scale chromatin structure and global transcriptional repression in pre-ovulatory oocytes will be discussed. Post-translational modifications of histone proteins such as acetylation and methylation are crucial for heterochromatin formation and thus play a key role in remodeling the oocyte genome. This strategy involves multiple and hierarchical chromatin modifications that regulate nuclear dynamics in response to a developmentally programmed signal(s), presumably of paracrine origin, before the resumption of meiosis. Models for the experimental manipulation of large-scale chromatin structure in vivo and in vitro will be instrumental to determine the key cellular pathways and oocyte-derived factors involved in genome-wide chromatin modifications. Importantly, analysis of the functional differentiation of chromatin structure in the oocyte genome with high resolution and in real time will have wide-ranging implications to understand the role of nuclear organization in meiosis, the events of nuclear reprogramming and the spatio-temporal regulation of gene expression during development and differentiation.
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Introduction

Purkinje's germinal vesicle: early descriptions of the mammalian oocyte nucleus

In 1825, Jan Evangelista Purkinje, then at the University of Breslaw, published a treaty entitled 'De evolutione vesiculae germinativae' (on the development of the germinal vesicle). Using only a hand-held lens, Purkinje described the presence and consistency of a vesicular structure in the hen's egg, which he named the *vesicula germinativa* (germinal vesicle) because he initially considered this 'vesicle' as an entire cell from which an embryo would subsequently arise and not as the cell nucleus. It was not until 1834 that Adolph Bernhardt, one of Purkinje's doctoral students, described a structure 'analogous to the germinal vesicle' in mammalian ova that the notion of the germinal vesicle as the oocyte nucleus emerged (Harris, 1999). Studying the graafian follicle of the sheep in 1835, Rudolph Wagner discovered the presence of a 'spot' within the germinal vesicle. Wagner speculated that the function of the structure he chose to call *macula germinativa* (germinal spot) was the origin or first stage in the development of the germinal vesicle. Although his observations provide the initial description of the nucleolus, the term itself was not introduced until 1839 by Gabriel Gustav Valentin, also Purkinje's close collaborator. In describing his observations on (Purkinje's) cells of the central nervous system, Valentin makes reference to the nucleolus as a 'rounded, transparent secondary nucleus' to describe the *macula germinativa* discovered by Wagner (Harris, 1999).

Although the term germinal vesicle has not lived up to the initial expectations of its nature as an embryonic rudiment, it is

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still widely used among reproductive biologists to denote the nucleus of mammalian oocytes. Perhaps it is only suiting that a cell nucleus with such a unique and specialized structure and function has retained such a *sui generis* designation.

Epigenetic modifications during oogenesis

In the mammalian neonatal ovary, oocytes are naturally arrested at prophase I of meiosis. From the onset of ovarian follicle activation, oocytes are maintained in a protracted meiotic arrest at the diplotene or dictyate stage during post-natal development. Meiotic arrest is maintained until puberty when the luteinizing hormone (LH) surge stimulates the resumption of meiosis in one or more oocytes depending on the species (Eppig et al., 2004). In the mouse ovary, the first wave of oocyte growth and differentiation is synchronous and is also the time at which maternal-specific genomic imprints are established on a locus by locus basis (Bourc'his et al., 2001; Eppig et al., 2004; Kono et al., 1996; Lucifero et al., 2004; Obata et al., 2002). This process of epigenetic modifications or 'epigenetic maturation' is capable of affecting gene expression without a change in DNA sequence and ultimately confers the mammalian genome with a sex-specific mark or genomic imprint essential for embryonic development (Barton et al., 1984; McGrath and Solter, 1984; Obata et al., 1998; Surani, 1998). The mechanisms underlying the developmental regulation of epigenetic modifications on specific loci are still not clear, however, they are the focus of intense investigation (Bourc'his et al., 2001; Fedoriw et al., 2004; Howell et al., 2001; Li, 2002; Morgan et al., 2005; Reik et al., 2001).

Importantly, the oocyte genome is also subject to additional levels of regulation, and functional differentiation of large-scale chromatin structure provides an important epigenetic mechanism for the developmental control of global gene expression (Eppig et al., 2004; Patterton and Wolffe, 1996). For example, recent studies indicate that, coincident with follicular activation, an oocyte-specific linker histone (H1foo) is loaded into the mouse oocyte nucleus (Tanaka et al., 2001; Tanaka et al., 2005) consistent with a possible role for multiple subtypes of linker histone H1 during oogenesis (Adenot et al., 2000; Fu et al., 2003; Wiekowski et al., 1997). Moreover, dynamic changes in chromatin structure and function occur during oocyte growth in several mammalian species. Morphological transitions in the GV were originally recognized in human (Parfenov et al., 1989), monkey (Lefevre et al., 1989), rat (Mandl, 1962), mouse (Chouinard, 1975) and pig oocytes (McGaughey et al., 1979). However, Mattson and Albertini provided the initial evidence for sequential changes in chromatin organization during folliculogenesis in the mouse and described the formation, coincident with follicular antrum differentiation, of a perinucleolar chromatin rim in the GV (Mattson and Albertini, 1990). Subsequent studies confirmed that chromatin in growing mouse oocytes (Fig. 1A) is initially found decondensed in a configuration termed Non-surrounded nucleolus (NSN) (Debey et al., 1993). Furthermore, these studies provided additional evidence indicating that, with

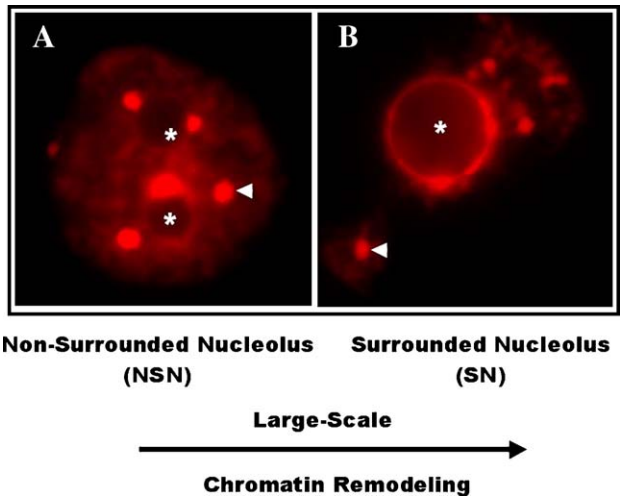

Fig. 1. Chromatin configuration in the germinal vesicle (GV) of fully grown mouse oocytes. (A) Representative micrograph illustrating a decondensed chromatin configuration (Non-surrounded nucleolus; NSN) with prominent heterochromatin regions (arrowhead). The position of the nucleolus is indicated by (*). DNA was stained with Hoechst 33248 and shown in red. (B) Chromatin condensation around the nucleolus (Surrounded nucleolus; SN) is associated with the formation of a heterochromatin rim or karyosphere (100×). Similar large-scale chromatin remodeling events have been described in oocytes of several mammalian species.

subsequent growth and differentiation, oocytes undergo a dramatic change in nuclear organization in which chromatin becomes progressively condensed (Fig. 1B), forming a heterochromatin rim in close apposition with the nucleolus, thus acquiring a configuration termed Surrounded nucleolus (SN) (Debey et al., 1993; Zuccotti et al., 1995) or karyosphere (Parfenov et al., 1989). Notable exceptions to this process include the goat (Sui et al., 2005) and equine oocyte (Hinrichs and Williams, 1997) in which chromatin condensation acquires a different configuration during the final stages of oogenesis.

In the human and mouse *ovum*, these changes in large-scale chromatin structure are in turn associated with profound modifications in the metabolic status of the oocyte genome. For instance, oocytes with the NSN configuration exhibit high levels of transcription (Figs. 2A, B). In contrast, the acquisition of the SN configuration is associated with global repression of transcriptional activity in vivo (BouniolBaly et al., 1999; Miyara et al., 2003; Parfenov et al., 1989) as well as in cultured oocyte–granulosa cell complexes (De La Fuente and Eppig, 2001 and Figs. 2A–D). In addition, the transition into the SN configuration correlates with the timely progression of meiotic maturation (Debey et al., 1993; Schramm et al., 1993; Wickramasinghe et al., 1991) and with higher rates of blastocyst formation after in vitro fertilization of mouse oocytes (Zuccotti et al., 1998). Thus, functional differentiation of chromatin structure in the GV provides the oocyte genome with an additional level for the control of transcription on a global scale. Importantly, changes in large-scale chromatin structure (at the chromosomal level) are essential to confer growing oocytes with meiotic and developmental competence.

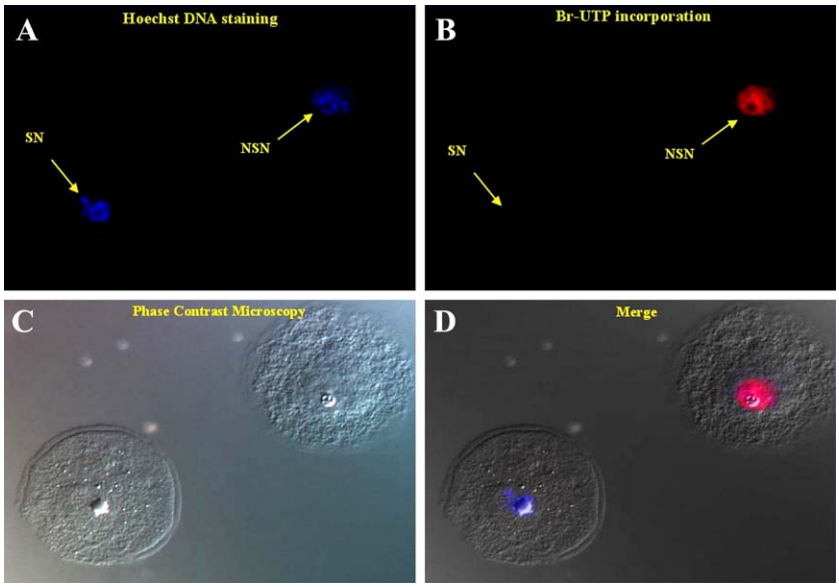

Fig. 2. Chromatin configuration and global transcriptional activity in mouse oocytes. (A) DNA staining of the two major types of chromatin configuration present in fully grown oocytes. (B) A decondensed (NSN) configuration is associated with active RNA synthesis as detected by the incorporation of bromo-UTP (Br-UTP) into nascent transcripts (red). The transition into the SN configuration is associated with global transcriptional repression as determined by the lack of Br-UTP incorporation in a different oocyte present in the same transcription run-on assay. (C) Phase contrast micrograph showing a vacuolated nucleolus in transcriptionally active oocytes and a condensed nucleolus in a transcriptionally quiescent oocyte (40×). (D) Merge.

Large-scale chromatin structure and global transcriptional repression

Following transcriptional silencing, pre-ovulatory oocytes rely on maternal messenger RNA (mRNA) stores to resume meiosis and sustain the first cleavage divisions after fertilization (Hodgman et al., 2001; Stebbinsboaz et al., 1996). Thus, the timing of transcriptional repression is critical for subsequent embryonic development. For example, experimentally extending the period between transcriptional repression in the GV and the onset of meiotic maturation for 4–6 days (equivalent to the length of one estrous cycle in mice) reduced the cleavage rates and the frequency of blastocyst formation in mouse embryos (De La Fuente and Eppig, 2001). This suggests that the developmental potential of transcriptionally quiescent pre-ovulatory oocytes maintained in an extended prophase arrest for more than one estrous cycle might be severely compromised. Therefore, synthesis and storage of viable, translationally dormant, maternal products before the onset of global transcriptional silencing, are essential for the oocyte's acquisition of developmental competence.

In spite of its biological significance, little is known concerning the cell signaling pathways and molecules involved in coordinating changes in large-scale chromatin structure, such as the transition into the SN configuration, with the onset of transcriptional repression. It is well established that, in mammalian somatic cells, transcriptional silencing occurs during the transit through mitosis (Gottesfeld and Forbes, 1997). However, global repression of transcription in the GV occurs long before germinal vesicle breakdown and the condensation of individual chromosomes. This suggests that, in contrast with somatic cells, unique strategies are set in place for the control of transcriptional silencing in pre-ovulatory oocytes. Using transgenic mice deficient for nucleoplasmin 2 ($Npm2^{-/-}$) (Burns et al., 2003; De La Fuente et al., 2004a), we have begun to dissect the relationship between the transition into the SN configuration and transcriptional repression in mammalian oocytes. Mouse Npm2 is the mammalian ortholog of *Xenopus laevis* (NPM2), a nuclear chaperone involved in remodeling sperm chromatin in *Xenopus* egg extracts. Oocytes from Npm2 knockout mice exhibit aberrant chromatin configuration (Burns et al., 2003) and thus provide a unique model to determine whether nuclear remodeling into the SN configuration is strictly required for transcriptional quiescence in the oocyte genome. Simultaneous analysis of chromatin configuration and global transcriptional activity using DNA fluorochromes and transcription run-on assays demonstrated that, although the transition into the SN configuration fails to occur in pre-ovulatory oocytes obtained from gonadotropin-stimulated Npm2 null females, global transcriptional activity is still repressed in the nucleoplasm of Npm2 deficient ova (De La Fuente et al., 2004a). It is important to emphasize that, although these oocytes exhibit disorganized nucleoli in large clusters of heterochromatin regions, chromatin in the nucleoplasm remains decondensed and at least morphologically resembles that of growing oocytes. These results indicate that remodeling chromatin into the SN configuration is not strictly required for global transcriptional repression in mammalian oocytes. Moreover, although these two processes occur concomitantly in wild-type pre-ovulatory oocytes, changes in large-scale chromatin structure and global transcriptional silencing can be experimentally

dissociated and are likely under the control of different pathways (De La Fuente et al., 2004a). These studies also provided the initial evidence indicating that, in addition to changes in large-scale chromatin structure, alternative mechanisms are set in place to induce transcriptional quiescence in the GV before the resumption of meiosis.

The primary mechanism(s) responsible for silencing the oocyte genome remain to be determined. However, it is conceivable that changes in the expression levels or nuclear availability of several transcription factors such as Sp1 and the TATA-box binding protein (TBP) (Worrad et al., 1994) or component molecules of the RNA polymerase II holoenzyme (Bellier et al., 1997; Gebara et al., 1997; Miyara et al., 2003; Parfenov et al., 2000, 2003) may halt ongoing nucleoplasmic transcription during the final stages of oocyte growth and differentiation even in the absence of the transition into the SN configuration. The complexity of this process, however, is illustrated by recent evidence indicating that different mechanisms seem to regulate ribosomal RNA (rRNA) transcriptional repression since the two subunits of RNA polymerase I, the upstream binding factor UBF as well as several proteins involved in both rRNA processing and ribosome biogenesis remain associated with the nucleolus even after the transition into the SN configuration (Zatsepina et al., 2000).

Evidence for a role of cumulus granulosa cells in the modulation of global transcription and large-scale chromatin structure in the GV

The initial indications of the potential involvement of companion granulosa cells in modulating large-scale chromatin remodeling during mammalian oocyte growth were obtained through the use of a unique system for the culture of mouse oocyte–granulosa cell complexes obtained from pre-antral follicles (Eppig and O'Brien, 1996). This system for in vitro gametogenesis sustains the synchronous acquisition of meiotic and developmental competence in a large number of oocytes and proved essential for the analysis of the critical window during oocyte growth when major changes in nuclear remodeling take place. For example, analysis of chromatin configuration and transcriptional activity in cultured oocyte–granulosa cell complexes demonstrated that transcriptional repression and the concomitant transition into the SN configuration occur in >87% of in vitro grown oocytes at an equivalent chronological stage compared with in vivo derived ova. However, in the absence of a patent gap junctional communication with somatic granulosa cells, transcriptional activity remained unabated in denuded oocytes (De La Fuente and Eppig, 2001). These results provided the first experimental evidence suggesting that companion granulosa cells contribute with an as yet unidentified signal, presumably of paracrine origin that modulates transcription and large-scale chromatin remodeling in the oocyte genome (De La Fuente and Eppig, 2001). Subsequent studies have confirmed a role for cumulus granulosa cells in the modulation of transcription in the GV and suggested that transcriptional repression in fully grown mouse oocytes that exhibit the SN configuration correlates with higher rates of meiotic maturation to the metaphase II stage (Liu and Aoki, 2002). Oocyte growth and differentiation depend on the establishment of a patent bidirectional communication mediated by heterologous gap junctions between oocytes and companion granulosa cells during folliculogenesis (Eppig, 2001; Matzuk et al., 2002; Mehlmann et al., 2004). However, although cumulus granulosa cells have been shown to affect the phosphorylation of several oocyte-derived proteins (Cecconi et al., 1991; Colonna et al., 1989), the signal(s) emanating from cumulus cells that might be involved in remodeling chromatin in the GV remain to be determined. Nevertheless, accumulating evidence indicates that, at least in the mouse model, cumulus granulosa cells that remain in contact with the oocyte serve a critical role in the developmental regulation of global transcriptional silencing in pre-ovulatory oocytes.

Insights into the mechanisms of large-scale chromatin modifications in the GV: role of histone deacetylases (HDACs)

The mechanisms involved in the developmental modulation of large-scale chromatin remodeling in the GV are most likely part of a complex physiological process. However, in eukaryotic cells, multiple signaling pathways converge to induce post-translational modifications at specific amino acid residues of the core histone proteins (Cheung et al., 2000; Fischle et al., 2003; Jenuwein and Allis, 2001), thus multiple histone post-translational modifications such as phosphorylation (Peterson and Laniel, 2004), acetylation (Grunstein, 1997; Turner, 2000), methylation (Bannister et al., 2001; Peterson and Laniel, 2004), poly (ADP) ribosylation (Faraone-Mennella, 2005; Rouleau et al., 2004) and ubiquitination (Zhang, 2003) play an essential role in the regulation of gene expression in response to environmental stimuli (Cheung et al., 2000; Jaenisch and Bird, 2003). Histone modifications may also result from changes in the metabolic state of a cell or as a response to extracellular signals and therefore constitute an efficient system to enhance the processing of genetic information (Cheung et al., 2000; Grunstein, 1997; Wolffe and Pruss, 1996). Binding of different histone variants to the chromatin template as well as post-translational modifications in the amino terminal domain of histone tails contributes to the establishment of epigenetic modifications in the mammalian genome (Jenuwein and Allis, 2001; Sarma and Reinberg, 2005). In turn, modifications of histone tails function to induce the formation of euchromatin or heterochromatin domains depending on the "context" of histone and nucleosomal interactions. For example, di-methylation of histone H3 at lysine 4 (H3K4 Me) is associated with transcriptionally permissive euchromatic regions of the mammalian genome but is excluded from transcriptionally silent heterochromatin domains (Santos-Rosa et al., 2002). In contrast, tri-methylation of lysine 9 on histone H3 (H3K9 Me) is exclusively associated with centromeric heterochromatin (Bannister et al., 2001). Such an epigenetic state is stable, heritable through cell division and essential to maintain the patterns of gene expression (Michelotti et al., 1997; Turner, 2000).

Histone acetylation is associated with modifications in higher order chromatin structure whereby an 'open' chromatin configuration in the nucleosome results in enhanced transcriptional activity. Importantly, acetylation of histone H4 at lysine 5 (H4K5 Ac) is associated with the maximum level of acetylation on histone H4 (Cheung et al., 2000; Grunstein, 1997; Turner, 2000; Wolffe and Pruss, 1996). In contrast, histone deacetylases (HDACs) have the potential for inducing transcriptional repression at promoter regions of target genes or to induce chromatin modifications over several Kb sequences and thus potentially determine different patterns of chromatin structure across the *Drosophila* genome (Ekwall et al., 1997; Fuks et al., 2001; Grunstein, 1997; Turner, 2000). Further evidence indicates that HDACs may also be essential for the regulation of gene expression during developmental transitions affecting embryonic patterning in *C. elegans* and *Drosophila* (Ahringer, 2000).

Importantly, HDACs also seem to participate in the maintenance of the SN configuration in the GV of mouse oocytes (De La Fuente et al., 2004a). Inhibition of HDACs activity with trichostatin A in pre-ovulatory oocytes that exhibit the SN configuration resulted in a striking decondensation of euchromatin regions within 8 h of treatment (Fig. 3). Interestingly, centromeric heterochromatin associated with the nucleolus showed only a partial response to TSA exposure (De La Fuente et al., 2004a). HDACs are also critical to regulate essential aspects of large-scale chromatin remodeling during meiosis as indicated by recent evidence suggesting the existence of a wave of genome-wide histone deacetylation taking place upon meiotic resumption (De La Fuente et al., 2004b; Kim et al., 2003; Sarmento et al., 2004).

Genome-wide histone deacetylation at several lysine residues has been demonstrated in mitotic cells (Kruhlak et al., 2001) and upon resumption of meiosis in mouse (De La Fuente et al., 2004b; Kim et al., 2003; Sarmento et al., 2004) and pig oocytes (Endo et al., 2005). This is consistent with the notion that the basic mechanisms of chromatin modifications have been evolutionarily conserved in mammals (Bannister et al., 2001; Lachner et al., 2001; Rea et al., 2000). Histone deacetylases have been implicated in the establishment of chromatin marks required for stable maintenance of chromosome structure and function through cell division (Ekwall et al., 1997; Taddei et al., 2001). Chromatin modifications, however, are multiple and complex, and several post-translational modifications at different amino acid residues of the histone protein may take place simultaneously to determine a biological response or a developmental transition (Jenuwein and Allis, 2001). For example, deacetylation of histone H4 at lysine 12 (H4K12) occurs coincident with the onset of meiosis in mouse oocytes but not during mitotic cell division (Kim et al., 2003). Similar mechanisms exist in the mouse oocyte that induce the removal of arginine methylation from histones H3/H4 in condensing meiotic chromosomes (Sarmento et al., 2004), a process that might be of biological significance for genome reprogramming in the female gamete (Akiyama et al., 2004; Kim et al., 2003; Kruhlak et al., 2001).

Evidence has also been provided for a role of HDACs in the epigenetic control of heterochromatin formation in *S. pombe*, *Drosophila* (Ekwall et al., 1997; Karpen and Allshire, 1997) and, more recently, in human mitotic cells (Taddei et al., 2001) and mouse oocytes (De La Fuente et al., 2004a,b) where global changes in histone H3/H4 acetylation regulated by HDACs may be critical to determine the localization of heterochromatin binding proteins to specific sub-domains in mammalian chromosomes (De La Fuente et al., 2004a; Taddei et al., 2001). For example,

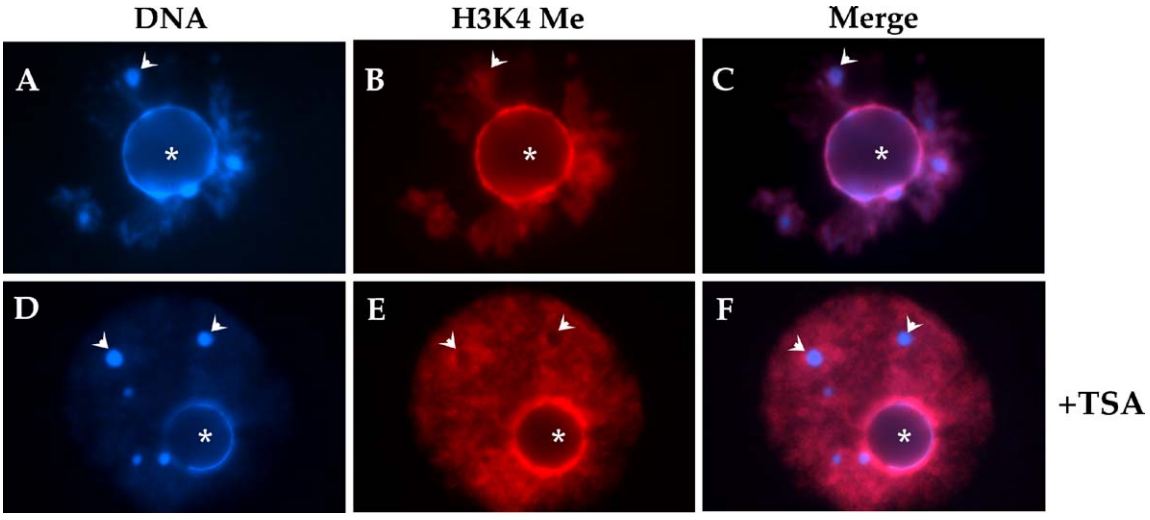

Fig. 3. Role of histone deacetylases in large-scale chromatin remodeling in the GV. (A) The nucleus of a pre-ovulatory oocyte showing the SN configuration. DNA was stained with Hoechst 33248 and shown in blue. The position of the nucleolus is indicated by (*). Heterochromatin domains can be distinguished by their intense Hoechst fluorescence (arrowhead). (B) Corresponding micrograph showing staining patterns for histone H3 di-methylated at lysine 4 (H3K4 Me) in the oocyte genome. (C) Merge (100×). (D) Striking chromatin decondensation induced by treatment of pre-ovulatory oocytes with 150 nM trichostatin A (+TSA). (E) Simultaneous staining with a monoclonal antibody against H3K4 Me reveals highly decondensed euchromatin fibers occupying the entire volume of the GV. Importantly, heterochromatin domains (arrowheads) lack H3K4 Me staining. (F) Merge (100×). Consistent with its role in euchromatin formation, H3K4 Me is excluded from heterochromatin domains in the mammalian oocyte genome.

underacetylation of histone H4 at lysine 5 (H4K5) at pericentric heterochromatin is essential to recruit heterochromatin protein 1 (HP1) specifically to the centromere of mitotic chromosomes in both human and murine somatic cells (Taddei et al., 2001). Moreover, studies conducted in mouse oocytes indicate that genome-wide histone deacetylation during meiosis is essential for the binding of ATRX (a chromatin remodeling protein) to centromeric heterochromatin in condensed chromosomes (De La Fuente et al., 2004b). Consistent with this hypothesis, pharmacological inhibition of HDACs with TSA during meiosis induced chromosome hyperacetylation, disrupted the binding of ATRX to centromeric domains and resulted in the formation of abnormal chromosome alignments at the meiotic spindle (De La Fuente et al., 2004b). These observations indicate that HDACs are involved in modulating non-targeted modifications in large-scale chromatin structure in the GV and that this process is essential for the progression of meiosis.

The nature of the specific HDACs involved in genome-wide chromatin modifications in the GV of mammalian oocytes is not known at present. Three major subclasses of HDACs have been described to date (Ahringer, 2000; Thiagalingam et al., 2003), members of the Class I, yeast *Rpd3p*-like deacetylase family (HDAC1, -2, -3 and 8), members of class II HDACs sharing homology with yeast *Hda1p* (HDAC 4,-5,-6,-7,-9 and 10) as well as the recently described mammalian homologues of yeast SIR2 which form a distinct class of NAD-dependent deacetylases suggested to play a role in chromatin remodeling (Thiagalingam et al., 2003; Verdel and Khochbin, 1999). Interestingly, over-expression of HDAC6 induced premature chromatin condensation in the GV as well as both male and female pronuclei in fertilized oocytes (Verdel et al., 2003). Moreover, previous studies indicate that members of the Class I, yeast *Rpd3p*-like family (HDAC1, -2 and -3) may be involved in transcriptional repression at regulatory sequences of reporter genes (Hassig et al., 1998; Kadosh and Struhl, 1998; Taunton et al., 1996; Yang et al., 1996).

Histone methylation and the transition to the first mitosis

In contrast to the dynamic nature of histone modifications induced by HDACs (Katan-Khaykovich and Struhl, 2002; Kouzarides, 2000; Vogelauer et al., 2000), changes in chromatin modifications induced by histone and DNA methylation are very stable and, as such, have the potential to stabilize epigenetic modifications through critical developmental transitions (Bannister et al., 2002; Kubicek and Jenuwein, 2004). Therefore, changes in genome-wide histone acetylation and/or methylation during oogenesis (Fig. 4) may contribute to the establishment and/or maintenance of epigenetic asymmetry between the paternal and maternal genomes after fertilization. The range of chromatin modifications taking place specifically in the maternal or paternal genomes of the mouse zygote has been reviewed elsewhere (Chang et al., 2005; Morgan et al., 2005). Differences in chromatin modifications between the maternal and paternal pronucleus result in both hyperacetylation (Adenot et al., 1997) and global histone demethylation in the paternal pronucleus (Arney et al., 2002; Erhardt et al., 2003; Liu et al., 2004; Santos et al., 2005) as well as demethylation of CpG islands on sperm-derived single-copy genes (Mayer et al., 2000; Oswald et al., 2000). The mechanisms responsible for protecting the maternal genome from histone and DNA demethylation immediately after fertilization are not clear at present. However, di-methylation of histone H3 at lysine 9 (H3K9) in the maternal genome has been recently suggested to have a role in preventing histone demethylation in the female pronucleus during the first cell cycle (Morgan et al., 2005; Santos et al., 2005).

Identification of the role of specific histone demethylases involved in global chromatin modifications in mammalian gametes and embryos will have major implications for our understanding of the mechanisms regulating genome reprogramming during mammalian development (Hajkova et al., 2002; Li, 2002; Morgan et al., 2005; Reik et al., 2001; Surani, 2001) and to determine the potential impact of epigenetic asymmetry between paternal and maternal genomes in lineage commitment during cell differentiation (Reik and Lewis, 2005; Rossant and Tam, 2004). However, characterization of histone demethylases in mammalian cells has remained elusive until the recent identification of several proteins capable of inducing demethylation of arginine (Cuthbert et al., 2004; Wang et al., 2004) or lysine residues (Shi et al., 2004) of histones H3/H4. Elimination of the methylated arginine 3 residues of histone H4 is catalyzed by the peptidyl arginine deimidase (PAD) enzyme in several human cell lines (Cuthbert et al., 2004; Wang et al., 2004). Moreover, PAD is expressed in mouse oocytes, where it has been suggested to play a role in the removal of methylated arginine 3 of histone H4 from condensing chromosomes after the resumption of meiosis (Sarmento et al., 2004; Wright et al., 2003). Importantly, the first bona fide lysine-specific demethylase (LSD1) has been recently described (Shi et al., 2004). LSD1 has been evolutionarily conserved from yeast to human, and several lines of evidence indicate that it is specifically involved in demethylation of lysine 4 on histone H3 at promoter regions of neuronal and cell cycle regulatory genes in mammals (Shi et al., 2004). However, LSD1 does not seem to be involved in the control of global or genome-wide H3K4 methylation (Shi et al., 2004). In addition, the expression of two cytidine deaminases (AID and Apobec 1) with potential for demethylating 5-methyl cytosine residues in DNA has been recently detected in mouse oocytes, primordial germ cells and embryonic stem cells (Morgan et al., 2004). The potential involvement of any of these novel histone demethylases in the establishment of epigenetic asymmetry between parental genomes remains to be demonstrated.

Conclusions

The mammalian oocyte nucleus is subject to multiple levels of regulation for the control of gene expression (Fig. 5). For example, cycles of cytoplasmic polyadenylation and deadenylation in regulatory sequences determine the selective expression and/or accumulation of dormant maternal

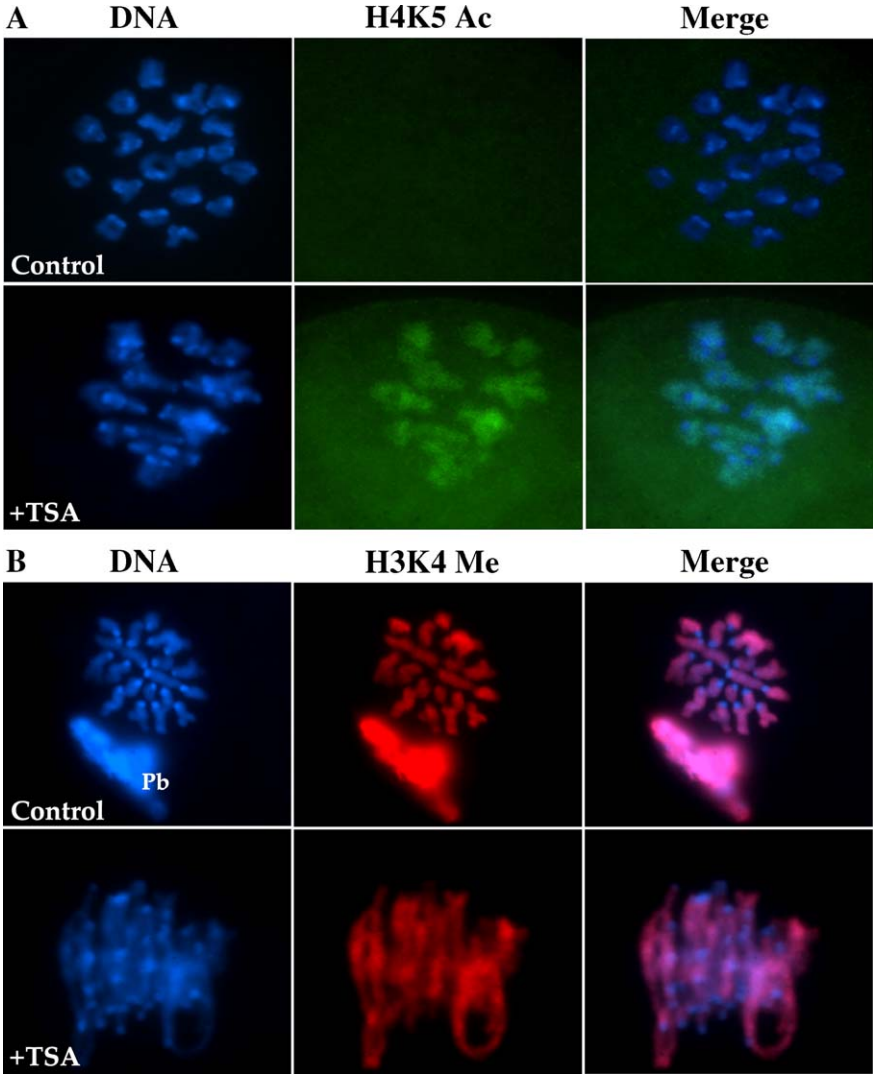

Fig. 4. Dynamic changes in global histone acetylation during meiosis. (A) Resumption of meiosis is associated with a wave of genome-wide histone deacetylation at several lysine residues for histones H3/H4 (upper panel). Inhibition of histone deacetylases (HDACs) in maturing oocytes after exposure to trichostatin A (TSA) induces hyperacetylation of histone H4 at lysine 5 (H4K5 Ac; green) in meiotic chromosomes (lower panel). H4K5 Ac is associated with the maximum level of histone H4 acetylation, and removal of this lysine modification by genome-wide deacetylation during meiosis is essential to recruit heterochromatin-binding proteins to centromeric domains. (B) In contrast with the rapid transitions in histone deacetylation, histone methylation marks are stable and transmitted through meiotic cell division. For example, methylation of histone H3 at lysine 4 (H3K4 Me; red) is restricted to the chromatids of meiotic chromosomes in oocytes at the metaphase II stage (note that all centromeres are stained in blue; upper panel). Importantly, centromeric heterochromatin domains lack H3K4 Me, even after exposure of oocytes to TSA (lower panel). Although TSA induced abnormal chromosome morphology, the epigenetic mark provided by H3K4 Me is still restricted to the chromatids of individual chromosomes and is not spread over centromeric heterochromatin domains. The position of the polar body (Pb) on a metaphase II stage oocyte is indicated.

transcripts essential to sustain the progression of meiosis and the first cleavage division (Groisman et al., 2002; Hodgman et al., 2001). Gene-specific regulatory elements acting in (*cis*) induce 'local' changes in DNA methylation that are associated with targeted modifications in chromatin structure and function at promoter regions (Fedoriw et al., 2004). Importantly, recent evidence indicates that superimposed on the 'local' control mechanisms regulating expression of individual loci lays an important non-targeted strategy for the control of transcription at the global scale. This strategy involves multiple and hierarchical large-scale chromatin modifications that regulate global transcription before the onset of meiosis. Thus, chromatin modifications and remodeling occur not only at specific promoter regions and *cis*-acting regulatory elements of single-copy genes but also throughout large sections of the genome (Berger and Felsenfeld, 2001; Vogelauer et al., 2000).

However, in direct contrast with our current understanding of the 'local' chromatin-dependent mechanisms that control single-copy gene expression in somatic cells (Narlikar et al., 2002), little is known concerning the unique molecular mechanisms involved in the regulation of large-scale chromatin structure and its impact on global transcription in the female germ line. Current models for the manipulation of large-scale chromatin structure in vivo (Npm2 knockout) as well as the pharmacological inhibition of HDACs suggest that the specific changes in global chromatin structure leading to the transition into the SN configuration, although dispensable

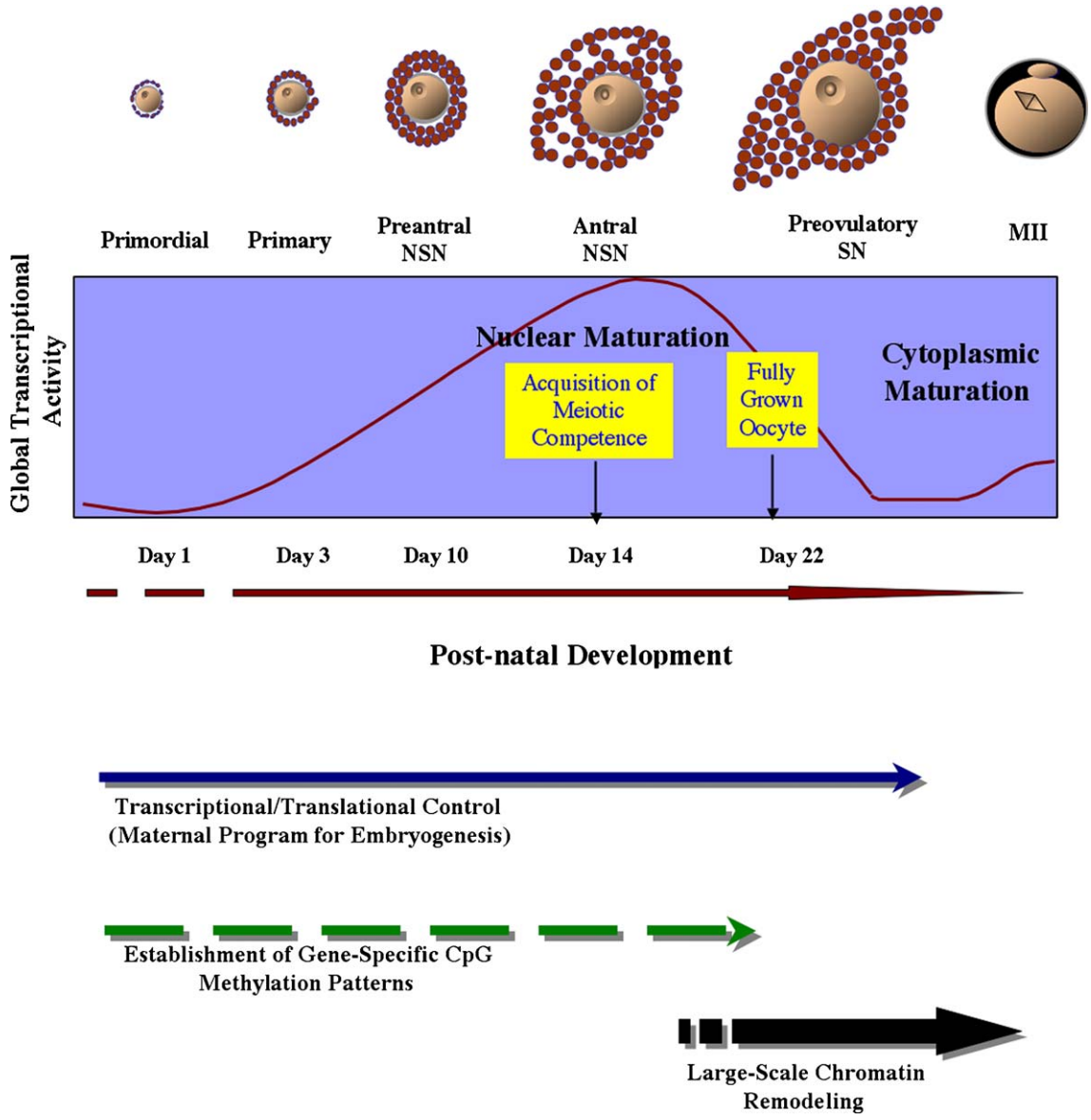

Fig. 5. Functional differentiation of chromatin structure during mouse oocyte growth. Coordinated transcription and translational control mechanisms regulate single-copy gene expression in the oocyte genome. Synthesis and storage of dormant maternal mRNAs during oogenesis are essential for the completion of meiosis and pre-implantation development. During oocyte growth, establishment of maternal-specific imprints occurs on a locus-by-locus basis through the methylation of CpG dinucleotides present within regulatory DNA sequences of single-copy genes. Coincident with the formation of antral follicles on day 14 of post-natal development, oocytes acquire meiotic competence. At this stage, the oocyte genome is at the peak of its global transcriptional activity. From day 17 of post-natal development onwards, subsequent oocyte growth and differentiation are associated with the onset of large-scale chromatin remodeling, leading to the transition into the SN configuration and global transcriptional quiescence in a cohort of pre-ovulatory oocytes. Although the mechanisms regulating large-scale chromatin remodeling in the GV are not known, current models for in vitro gametogenesis together with experimental manipulation of global chromatin structure in vivo and in vitro provide a unique experimental paradigm to address these pathways.

for transcriptional repression, may confer specific chromatin domains with a functional configuration to recruit hetero-chromatin binding proteins and hence play an essential role in the progression of meiosis and perhaps in reinforcing the transcriptional quiescence of a pre-ovulatory oocyte.

Whether subtle changes at the level of the 30 nm DNA fiber or its tertiary folding take place during transcriptional repression in the mouse oocyte genome remains to be determined. Prospects are in sight for the application of novel live cell imaging analysis methods that will allow a three-dimensional reconstruction of the nuclear environment with high resolution (perhaps at the level of 30–100 nm) and in real time (O'Brien et al., 2003) in order to gain a better understanding of how the 'histone code' (Jenuwein and Allis, 2001) or changes in nucleosome structure brought about by ATP-dependent chromatin remodeling complexes (Berger and Felsenfeld, 2001; Vogelauer et al., 2000) may impact large-scale chromatin structure in the mammalian germ line. Such a 'glimpse' at the spatial arrangements of chromosomes in live cells will contribute with invaluable new information towards a better understanding of the events involved in genome reprogramming after somatic cell nuclear transfer (Gao et al., 2004; Teranishi et

al., 2004; Wade and Kikyo, 2002). For example, recent studies on protein dynamics revealed that the mammalian cell nucleus is in a continual state of flux. Thus, in addition to providing a strategic advantage to mount a rapid response to environmental signals or a specific developmental transition, dynamic changes in nuclear architecture also provide the natural basis for genomic plasticity (Chubb and Bickmore, 2003; Wolffe and Hansen, 2001).

Integrating information obtained from studies of chromatin organization on single-copy genes (local) and large-scale with high resolution and in real time will also be critical to understand the spatio-temporal regulation of gene expression during development and differentiation (Hamatani et al., 2004a; O'Brien et al., 2003; Zeng and Schultz, 2005). Importantly, studies on chromatin modifications during mammalian oocyte growth will have wide-ranging implications for our understanding of the role of nuclear architecture in the progression of meiosis as well as the mechanisms leading to genomic instability in the female germ line. For example, the expression of genes encoding several chromatin-binding proteins and DNA methyltransferases has recently been shown to be down-regulated in aging mouse oocytes (Hamatani et al., 2004b). Thus, a better understanding of the cellular and molecular mechanisms regulating chromatin modifications in fully grown mammalian oocytes is needed in order to shed new light into both intrinsic and environmental factors that might predispose the female gamete to the onset of aneuploidy.

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