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Accumulation of chromatin remodelling enzyme and histone transcripts in bovine oocytes

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Short title: mRNA content of histones and remodeling enzymes in oocytes

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Abstract

During growth, the oocyte accumulates mRNAs that will be required in the later stages of oogenesis and early embryogenesis until the activation of the embryonic genome. Each of these developmental stages is controlled by multiple regulatory mechanisms that ensure proper protein production. Thus mRNAs are stabilized, stored, recruited, poly-adenylated, translated and/or degraded over a period of several days. As a consequence, understanding the biological significance of changes in the abundance of transcripts during oocyte growth and differentiation is rather complex. Nevertheless the availability of transcriptomic platforms applicable to scarce samples such as oocytes, has generated large amounts of data that depict the transciptome of oocytes under different conditions. Despite several technical constrains related to protein determination in oocytes that still limit the possibility to verify certain hypothesis, it is now possible to use mRNA levels to start building plausible scenarios. To start deciphering the changes in the level of specific mRNAs involved in chromatin remodelling while, we have performed a meta-analyses of existing microarray datasets from Germinal Vesicle (GV) stage bovine oocytes during the final stages of oocyte differentiation. We then analyzed the expression profiles of histone and histone remodelling enzyme mRNAs and correlated these with the major histone modifications known to occur at the same period, based on data available in the literature. We believe that this approach could reveal the function of specific enzymes in the oocyte. In turn, this information will be useful in future studies, which final ambitious goal is to decipher the 'oocyte-specific histone code'.

Key words: Bovine, oocyte, chromatin configuration, germinal vesicle, transcriptome, histone, mRNA epigenetic modification

1. Premise*

*Please also refer to (Leung and Adashi 2003) and (Hyttel 2010) as general bibliographic references for the premise.

Mammalian oocytes enter meiotic prophase I during fetal life. In the fetus, the meiotic cell cycle arrests at the diplotene stage of prophase I until after puberty. When meiotic cell cycle arrests, a single layer of flattened granulosa cells surround the oocytes, thus forming the primordial follicles. These follicles are quiescent and constitute a pool from where they will be recruited for growth (follicle activation) and cyclically selected for ovulation during reproductive life. During subsequent follicle development (see below), the growth phase of the oocytes occurs, and their diameters increase considerably. Once the growth phase is concluded, the sole 'fully-grown' oocytes selected for ovulation resume meiosis in response to luteinizing hormone (LH), while subordinate follicles, enclosing oocytes that have not been selected for ovulation, undergo degeneration through atresia (Scaramuzzi et al. 2011; Gougeon 1986). Upon meiotic resumption, which occurs only after puberty is reached, meiosis continues to the metaphase of meiosis II (MII stage), occurring when the oocytes are released from the follicles. In mono-ovulatory species such as cattle, one MII stage per reproductive cycle is released, whereas the remaining follicles undergo atresia. On the contrary in poly-ovulatory species, such as mouse, multiple oocytes are released. Oogenesis and folliculogenesis are linked with the oocyte growing and developing in an intimate and mutually dependent relationship with the somatic cells of the follicle. Folliculogenesis progresses through sequential stages, leading to the formation and development of a fluid-filled cavity called the antrum (antral follicle stage), which also increases in size.

The nucleus of oocytes arrested at the diplotene I stage of meiosis is surrounded by an intact nuclear envelope and is named germinal vesicle (GV). Thus the expression 'GV stage' is often used to indicate when the oocyte is collected from the ovarian follicle before meiotic resumption occurs. During meiotic

arrest, and particularly during the final oocyte growth phase leading to the formation of the fully-grown and differentiated oocyte, the chromatin enclosed within the GV is subjected profound morphological, structural and functional remodeling (De La Fuente 2006; Luciano and Lodde 2013). Thus, GV stage oocytes can be further subdivided according to the level of chromatin compaction, which can be observed under fluorescence microscopy. This is biologically relevant since chromatin configuration is considered a marker of oocyte differentiation and developmental competence in all the species studied so far (De La Fuente 2006; Luciano and Lodde 2013)

As summarized in Figure 1, in cow four GV stages oocytes have been characterized (from GV0 to GV3), with increasing level of chromatin compaction (Lodde et al. 2007). GV0 oocytes, which typically show uncondensed chromatin, are found in early antral follicles (0.5-2 mm), while they are absent in antral follicle larger than 2 mm. In contrast, oocytes with increasing levels of compaction (GV1, GV2 and GV3) are typically collected from medium antral follicle >2 mm in diameter (Lodde et al. 2007). Importantly, we have recently shown that once the GV1 stage is reached, chromatin remodeling is not strictly related to follicular size. Indeed the percentages of GV1, GV2 and GV3 stages oocytes were similar in 2-4 mm, 4-6 mm and >6 mm antral follicle (Dieci et al. 2016).

In mice (Fig. 1), oocytes with uncondensed chromatin are referred to as 'Non Surrounded Nucleolus' (NSN) oocytes, while oocytes with compacted chromatin are referred to as 'Surrounded Nucleolus' (SN) oocytes (De La Fuente 2006; Luciano and Lodde 2013). Compared to bovine, a less precise relationship between chromatin configuration and follicular size is described in mice.

2. Introduction

The preparation of a mammalian oocyte for ovulation is a long and complex process that may take several months but can be divided in three important periods: growth, final differentiation, and meiotic resumption. The period of growth starts with activation of the primordial follicle into an activated one.

This is an irreversible process that will lead to atresia or ovulation in a period of several weeks in rodents or several months in large mammals. During growth, the oocyte transcription machinery is very active as the cell accumulates organelles, new structures such as the zona pellucida, and RNAs that will be required when growth eventually ceases in the antral follicle. Timing of completion of the growth phase and of transcriptional inactivation in relation to follicular development is species-dependent. Thus, for example, the growth of mouse oocytes is already completed in the early antral follicles (Sorensen and Wassarman 1976) while bovine oocytes are still in their growth phase (Dieci et al. 2016; Lodde et al. 2008). As follicular growth progresses into follicular differentiation, either in the process of atresia or in dominant and pre-ovulatory follicles, the oocyte transcription capacity decreases and eventually stops few hours before ovulation (Hunter and Moor 1987) in preparation for meiotic resumption. In this last phase, which is strictly regulated by post-transcriptional events, stored mRNAs are the only source of information for translation

Due to the transcriptional silencing, the oocyte relies on previously stored mRNAs for protein formation as the proteins have a limited half-life. The amount of mRNA that oocytes accumulate starts to increase significantly when follicles reach the multilayer phase of development (Fair et al. 1997). Normally, mRNA is translated within hours; therefore, the accumulation of mRNA in oocytes requires a protection mechanism that evolved in animals producing eggs. In Xenopus, one of the proposed mechanisms involves the storage of maternal RNA using a specific configuration where the mRNA is de-polyadenylated on the 3' end and capped on the 5' end. In this species, the protein MASKIN associates with the cytoplasmic polyadenylation element binding protein (CPEB) located in the 3' untranslated region (UTR) region on mRNAs that contain a cytoplasmic polyadenylation element (CPE) which represses translation through the inhibitory action on elF4E (Richter 2007). The recruitment of mRNA for translation is associated with longer polyA tails (more than 100 A) while mRNAs with shorter tails (around 20 A) are not recruited (Richter 2007). These mechanisms are conserved in rodents (Clarke 2012; Conti et al. 2015) as well as in large mammals. For instance, we recently surveyed bovine oocytes to

identify mRNAs with very long or very short polyA tails as indicators of the timing of translation during meiotic resumption (Gohin et al. 2014). This study led to the confirmation of cis-motifs as regulators of re-polyadenylation of maternal RNAs and to the identification of new sequences potentially involved in embryonic genome activation (Gohin et al. 2014). This study also illustrated quite clearly that some RNAs are translated during maturation while others remain in storage for the early embryonic period. In another study from our group, the analysis of polysomes from oocytes at the beginning versus the end of maturation confirmed the specific nature of recruitment and translation in bovine oocytes (Scantland et al. 2011). In addition we accumulated data from the analyses of bovine oocyte transcriptomic signatures in different physiological contexts, using the platform within the EmbryoGENE program (http://emb-bioinfo.fsaa.ulaval.ca (Robert et al. 2011)) that offers the unique opportunity to conduct meta-analysis across different datasets.

The availability of all the above-mentioned information becomes a key factor to assess the role of different histones transcripts or histones modifying enzymes in the oocyte. However, since oocytes are available in limited supply, the capacity to analyse protein amounts is limited and most studies relied on the amplification of mRNA through primers bearing a T7 promoter, or reverse transcription followed by PCR, to obtain information of the oocyte transcriptome. If this process is quite reliable in somatic cells, it becomes problematic in oocytes not only because of the limited supply of material but also because RNA is stabilized, stored, poly-adenylated, recruited, and translated or degraded over a period of several days from the transcriptional arrest to the embryonic genome activation, which occurs at the 8-cell stage in bovine (Barnes and First 1991). Because mRNA is stored de-polydeanylated, the length of the polyA tail is an issue for measurements. If the tail is short, the extraction protocols that use the capturing ability of poly T columns or filters are not efficient. Then, if the primers used for the reverse transcription include a poly T sequence, it will not include the stored RNA, and finally, if a T7 polymerase-based approach is used for RNA amplification (such as in microarray experiments), the presence of a polyA tail will exclude some non-polyadenylated RNAs. Therefore, careful attention must be given to the interpretation of RNA

levels obtained with these techniques prior to the 8-cell stage. These considerations have been clearly demonstrated in the past (Gilbert et al. 2009) and we will not use terms such as up-regulation or over-expression in this review unless the protein level has been verified by other means.

To start deciphering the changes in the levels of specific mRNAs involved in chromatin remodelling, and to try to overcome the above mentioned limitations, we have analyzed the expression profiles of histone and histone remodelling enzyme mRNAs in bovine GV oocytes during the final stages of oocyte differentiation (which is a critical step in the acquisition of the competence to sustain embryonic development) and correlated these with the major histone modifications (mainly methylation and acetylation) known to occur at the same period, based on data available in the literature. In particular, the list of genes that we considered in this review was generated by conducting a meta-analysis of two datasets from previous published studies: one from oocytes isolated from small (0.5-2 mm) and middle (2-8 mm) antral follicles and selected according to the degree of large scale chromatin configuration (Labrecque et al. 2015b), and one from oocytes isolated from follicles of different sizes (<3 mm; 3-5 mm; 5-8 mm; >8 mm) (Labrecque et al. 2016). From the list of genes obtained by the meta analysis, which basically represent the transcripts that are not randomly expressed during competence acquisition, and thus potentially important before meiotic resumption and ovulation, we arbitrarily selected the histone and histone related genes. Then, the dynamic expression profile of each of the selected target was evaluated separately in the original microarray datasets in each of the different experimental setting (chromatin configuration or follicular size). These data are presented and discussed in the following paragraphs

3. Identification of histone and histone related mRNA targets

To identify specific mRNAs related to histones and histone modifying enzymes we first performed one meta-analysis using NetworkAnalyst (http://www.networkanalyst.ca/) (Xia et al. 2015) by combining two data sets derived from previous microarray-based transcriptomic analysis of oocytes with different

chromatin configurations (GV-0-1-2-3) (Labrecque et al. 2015a) or collected from follicles of different dimensions (<3mm, 3-5mm, 5-8mm, >8mm) (Labrecque et al. 2016). All data sets were generated using the EmbryoGENE bovine transcriptome microarray (Robert et al. 2011). Microarray gene expression data from these earlier studies were retrieved from the ELMA database (http://emb-bioinfo.fsaa.ulaval.ca/Home/index.html) and pooled together for meta-analysis. The analysis focused on a specific cell type within the ovarian follicle: the GV (germinal vesicle) stage oocyte. For the first data set, we contrasted GV0 (characterized by uncondensed chromatin configuration) versus GV1, GV2 and GV3 (which are characterized by increasing levels of chromatin compaction). For the second group, GV oocytes from follicles 3 to 5 mm, 5 to 8 mm and larger than 8 mm were compared to the <3 mm group. Data processing involved conversion of all gene probes to common "Entrez ID" according to the EmbryoGene platform annotation file. In cases where multiple probes or transcripts are mapped to the same gene, NetworkAnalyst summarized them into a single value for the corresponding gene performing an average of the values. All the datasets were already log2-transformed and normalised-within, so "quantile normalization" was performed in NetworkAnalyst. First of all, the program analyses individual microarray datasets separately and subsequently performs meta-analysis. Differential expression analysis of each dataset was performed individually using a moderated t test based on the Limma algorithm and a false discovery rate (FDR) of 0.05. This step was for reference purpose only. We performed meta-analysis using Fisher's method with a significance level of $p < 0.05$. Fisher's method of meta-analysis combines p-values from the multiple datasets independently of the sample size within each study (Xia et al. 2015).

The list of genes generated by the meta-analysis was used to arbitrarily select histone- or histone modifying enzyme-related targets. Then, each of these targets was searched in the original microarray dataset that is accessible through an interactive web interface (Khan et al. 2016), which has been updated to include data from oocytes and cumulus cells (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/). Finally, the expression profile of each target was extracted from the interactive web interface, which allowed the evaluation of both constitutive and isoform (where present) for each target. Thus, the dynamic expression

profile of each of the selected transcript (both constitutive and isoforms) was evaluated separately in each of the different experimental setting (chromatin configuration or follicular size).

4. Significance of histone remodelling enzyme and histone transcripts dynamics in bovine oocytes

The meta-analysis resulted in a list of 4340 targets affected (i.e. non randomly expressed) by the combination of chromatin status and follicular size (supplemental table 1). This list is substantially different from the combination of the two lists from each analysis (GV status and follicular size) that would have been obtained by simply generating a Venn diagram. From this list we arbitrarily selected the genes related to histones or histone modifying enzymes, for which we then extracted the profiles according to the original microarray data (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/). These candidate targets, grouped according to known families and their expression profiles in each experimental setting (chromatin configuration and follicle size), are represented on graphs (see below) and discussed in the following paragraphs.

The first observation is that most of the changes are occurring between the GV0 stage and the more condensed chromatin statuses (GV1, GV2, and GV3). This is not surprising as the process of chromatin compaction is accompanied by progressive changes to the chromatin, which require different histones (for example the oocyte specific linker histone H1oo) (Labrecque et al 2016) or histone modifications (reviewed in (Canovas and Ross 2016; Clarke and Vieux 2015; Pan et al. 2012)).

It is worth mentioning here that while GV0 oocytes can only be found in small antral follicles (0.5 to 2 mm), once the chromatin starts the compaction process (GV0 to GV1 transition) the follicular size has no clear influence on the GV status (1 -2 or 3), since it has been recently demonstrated that GV1, GV2, and GV3 are equally distributed in follicles of different sizes (i.e. follicles between 2-4, 4-6 and >6 mm in diameter) (Dieci et al. 2016). Thus, when looking at the profiles of individual targets derived from microarray data in each experimental settings, it is not surprising that one gene can be found significant in

one experimental setting but not in the other. Similarly, it is not surprising to observe different increasing or decreasing trends for a specific transcript in the two experimental settings.

4. 1 Transcripts encoding Histones Modifying Enzymes

Understanding the biological significance of changes in transcript abundance during chromatin remodelling, is not an easy task. As already mentioned, one of the limiting factor is scarcity of material and the lack of specific antibodies that make it very difficult to properly track the encoded protein. In addition, during the transition from uncondensed (GV0) to more compacted configuration (GV1-2-3), a major transcriptional silencing occurs in mouse and bovine oocytes (Bouniol-Baly et al. 1999; Lodde et al. 2008); (reviewed in (Luciano and Lodde 2013)), and increased or decreased levels of specific transcripts may be due to the specific methodological approach used and have multiple and diverse significances as summarized in Table 1. Moreover, while a major silencing occurs at the beginning of the chromatin compaction process in bovine and mouse oocytes (reviewed in (Luciano and Lodde 2013), a low level of transcription could still be detected in bovine oocytes with intermediate configurations (GV1 and GV2), while only oocytes with fully compacted chromatin (GV3) were found to be completely silent (Lodde et al. 2008).

Therefore, in an effort to interpret the major findings of the present meta-analysis, wherever possible, we compared the changes in the abundance of transcripts encoding for histone modifier enzymes with the expected phenotype (that is the change in the histone modification associated to the specific enzyme) whenever these data where available. Moreover, since the bovine data are lacking for most of the histone modifications, we have critically reviewed the literature and built, taking into consideration the species-specific differences in ovarian physiology, a “consensus table” within and across species to have a global view of histone modification changes as they occur during chromatin compaction in mammals (Table 2 and Table 3). This is possible since, as summarized in Figure 1, the process of large scale chromatin

remodeling, in which the chromatin of prophase I-arrested mammalian oocytes condenses and progressively rearranges passing through intermediate configurations, is a well conserved process in (and not limited to) mammalian species (reviewed in (Luciano and Lodde 2013).

Discussion of original and published data relative to several histone modifications and related enzymes is reported below. The main interpretative key being the following: if changes in mRNA level for a particular transcript match with the occurrence of the corresponding histone modification, than the encoded protein is translated and most likely is functioning in the oocyte. In contrast, if the change in the mRNA level does not correlate with any changes of the specific histone modification, than the mRNA is probably coding for proteins that are needed to processes that will occur later, during maturation or early embryonic development.

Since the precise description of level of histone modification marks in bovine oocytes isolated from antral follicles of different diameter are currently not available, most of the discussion is based on the comparison between histone modification and the corresponding enzyme mRNA as they occur in oocytes with different chromatin configuration, where a match between mRNA level and corresponding phenotype is possible. However, where relevant, we also took into consideration some of the mRNA variations observed during follicular growth. Unless otherwise indicated, the function of each gene refers to data available on gene card (http://www.genecards.org) and/or UniProt (http://www.uniprot.org) databases.

4.1.1 Transcripts related to histone H3 Lysine 27 trimethylation (H3K27me3)

Among the differentially expressed transcripts that encode for Lysine Demethylases (KDMs) during chromatin compaction (Fig 2A), *KDM6A* (also known as ubiquitously transcribed tetratricopeptide repeat X, UTX) is the only one that specifically demethylates H3K27 (Agger et al. 2007; Lan et al. 2007). Based on our analysis, no transcripts encoding H3K27-specific methylase change significantly in the conditions studied. Immunofluorescence studies revealed that the levels of H3K27me3 were high in fully grown bovine oocytes, decreased slightly during oocyte maturation (Table 2), steadily decreased after

289 fertilization to reach a nadir at the eight-cell stage, and then increased at the blastocyst stage (after
290 embryonic genome activation) (Ross et al. 2008). However, no data are available for the earlier stages of
291 oogenesis in this species. Nevertheless, in mouse oocytes, no major changes occur during chromatin
292 compaction as H3K27me3 is always detected in both centromeric chromatin and in the rest of chromatin
293 during the transition from the uncondensed 'Non Surrounded Nucleoulus' (NSN) configuration to the
294 'Compacted Surrounded Nucleoulus' (SN) stage, with only a little increase in the pericentromeric
295 chromatin (Table 2). This is also in agreement with more recent findings in mice using highly sensitive
296 chromatin immunoprecipitation-based techniques that revealed widespread deposition of H3K27me3 in
297 early growing oocytes (before establishment of the DNA methylome) and profound changes after
298 fertilization, but not during the later stages of oocyte differentiation (i.e. comparing oocytes from 2- and 8-
299 week old mice) (Zheng et al. 2016). Thus the lower amount of *KDM6A* in GV1 -2 -3 oocytes (when
300 compared to GV0) might indicate RNA degradation rather than translation and protein production since
301 H3K27me3 is maintained at this stage. De-adenylation can be excluded since *KDM6A* mRNA could not
302 be detected in fully grown bovine oocytes (and up to the blastocyst stage) using either random primers or
303 oligo-dT for RT-PCR (Canovas et al. 2012) or RNA-seq approaches (http://emb-
304 bioinfo.fsaa.ulaval.ca/IMAGE/). This supports the idea that *KDM6A* mRNA degradation is associated to
305 with chromatin compaction in bovine GV oocytes and it is not required during early development
306
307 The Jarid2/Jumonji (*JARID2*) transcript encodes a protein that is a component of the polycomb repressive
308 complex 2 (PRC2), which is essential for the development of multiple organs in mice, and is required for
309 embryonic stem cell (ESC) differentiation (Landeira and Fisher 2011). It was recently demonstrated that
310 PRC2 methylates JARID2 and, in turn, JARID2 methylation regulates H3K27me3 deposition during
311 mouse ESC differentiation (Sanulli et al. 2015).
312 Our data indicated that the abundance of this transcript is higher in more condensed GV stages (GV1-2-3)
313 and increased as follicle grew (Fig 2E and 2F). The transcripts seemed to accumulate until the zygotic
314 stage, to be translated between the 2- and 8-cell stage, which would match the reprogramming window

(http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/). However this hypothesis, as well the precise role of *JARID2* during oogenesis and early embryogenesis (before genome activation), still need to be explored.

4.1.2. Transcripts related to Histone H3 Lysine 4 mono, bi, or trimethylation (H3K4me1, H3K4me2, H3K4me3)

As shown in Fig 2A *KDM5C*, *KDM5B*, *KDM5B_3U1*, and *KDM1A* mRNAs are all present in lower amounts in GV1-2-3 compared to GV0 oocytes, while KDM5A mRNA is present in higher amount. All the enzymes encoded by these mRNAs specifically demethylate H3K4.

As for H3K27me, no data are available in bovine oocytes but data in mice indicate that H3K4me2 and me3 increase in the later stages of chromatin compaction (from intermediate to highly compacted SN oocytes, **Table 2**). This is in agreement with recent chromatin immunoprecipitation experiments showing that H3K4me3 is present in a pattern that the authors indicated as 'non-canonical' in fully-grown and metaphase II (MII) mouse oocytes, when compared to late-stage embryos (after embryonic genome activation) and a somatic tissue (cerebral cortex) (Zhang et al. 2016a). Specifically, the DNA sequences in which H3K4me3 is presents in fully grown and MII oocytes differ from the one in which is normally found in somatic tissues (Zhang et al. 2016a). Importantly, the same study shown that H3K4me3 remains largely in a canonical pattern in growing oocytes (collected from 7- and 15-day old mice) before adopting a non-canonical pattern in fully-grown oocytes from 8-week old mice. Moreover, the non-canonical H3K4me3 pattern in oocytes overlaps almost exclusively with partially methylated DNA domains (Zhang et al. 2016a), which further confirms emerging evidence that the modification state and sequence of DNA can affect the methylation states of accompanying histones in chromatin, and vice versa (Rose and Klose 2014). Notably, the global occurrence of non-canonical H3K4me3 coincided with genome silencing (Zhang et al. 2016a). To see H3K4me3, which is normally considered a permissive epigenetic mark in somatic cells, so well distributed in a transcriptionally silent cell could mean openness for reprogramming in a context where Pol–II is not active, but this hypothesis requires further investigation.

All together these data suggest that the H3K4me pattern is remodeled during final oocyte differentiation and that, on a global scale, its level increases, which implies that some methylation must be removed while some other must be established at specific DNA sites. Therefore for certain transcripts such as *KDM5B*, the lower abundance in GV1-2-3 could be related to translation and subsequent degradation, and to degradation without translation. The increase of *KDM5A* mRNA could be related to the activity of the protein in oocytes with higher compacted chromatin and/or increased accumulation for later use. Accordingly, KDM5B overexpression in fully-grown mouse oocytes with SN configuration (which are transcriptionally inactive) led to removal of H3K4me3 and transcription reoccurrence, while overexpression of KDM5A did not affect H3K4me3 and transcription (Zhang et al. 2016a). Accordingly, *KDM5B* mRNA was not detected in fully-grown bovine oocytes up to the genome activation at the 8-cell stage, while *KDM5A* mRNA was detected even before genome activation (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/).

For some other transcripts such as *KDM1A*, reduced levels in GV1-2-3 are potentially linked to de-adenylation for storage for later use (KDM1A is associated with H3K4me1, H3K4me2). In mouse oocytes, KDM1A of maternal origin was essential for chromatin modification and genome activation (Ancelin et al. 2016). Accordingly, in bovine, *KDM1A* mRNA was detected by RNA-seq at all stages up to the embryonic genome activation: it dropped at the early 8-cell stage and was up regulated after genome activation (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/).

Notably, the global H3K4me increase observed in mice did not correspond to major changes in mRNA encoding H3K4me-specific methylases during chromatin compaction. Indeed, both the constitutive *SETD3*, whose encoded protein methylates H3K4 and K36, and the variant form mRNA (*SETD3_V*) were not significantly affected by chromatin configuration changes (Fig. 2C). However these transcripts accumulated in a follicle size-dependent manner (Fig. 2D), which could be related to changes occurring in preparation for ovulation and potentially re-programming as suggested above.

Interestingly, *KDM1B* mRNA, which is also associated with H3K4me1 and H3K4me2 demethylation and doesn't change significantly in relation to chromatin configuration, was notably increased in follicles larger than 5 mm where the capacity to develop is slightly higher (Fig 2B). In mice, this gene was highly expressed in growing oocytes at the time where genomic imprints are established (Ciccone et al. 2009). More recent studies showed that KDM1B is the primary H3K4me2 demethylase required for imprinted CpG islands (CGI) and the methylation of imprinted germline differentially methylated regions (gDMRs) in the oocyte (Stewart et al. 2015). Knock out of the gene encoding KDM1B had no effect on mouse development and oogenesis. However, when both alleles were affected, KDM1B-deficient oocytes had higher levels of H3K4 methylation and embryos derived from these oocytes died before mid-gestation (Ciccone et al. 2009). Therefore we could speculate that proper imprinting may occur in bovine oocytes coincident to the rise of *KDM1B* levels and could have an impact on embryo survival.

4.1.3. Transcripts related to Histone H3 Lysine 9 mono, bi, or trimethylation (H3K9me1, H3K9me2, H3K9me3)

Some H3K9 methylases and demethylases transcripts were present in different amounts during chromatin compaction. Among the transcripts encoding demethylases (Fig. 2A), *KDM4C* (also known as JMJD2C), whose encoded protein demethylates H3K9me3 and H3K36me3 residues, was higher in GV1-2-3 compared to GV0.The constitutive *KDM4B* (H3K9me3-specific) did not change significantly, while amount of the alternative 3'UTR (*KDM4B_3U1*) was lower in GV1-2-3. Among the transcripts encoding methylases only *SETDB1*, a histone methyltransferase that specifically trimethylates H3K9, was significantly affected in GV1-2-3 (Fig. 2C). However, interpretation of the biological significance of these changes is complicated. In fact, although H3K9 methylation is generally considered a marker of pericentromeric heterochromatin forming chromocenters, all the data available on H3K9me1, H3K9me2, and H3K9me3 are based on immunofluorescence and precise localization of H3K9me deposition during oocyte and embryonic development is lacking. Moreover, data in the literature are sometimes

controversial. Nevertheless, both H3K9me2 and H3K9me3 were present in oocytes with less compacted chromatin with some increase during chromatin compaction, with H3K9me3 more clearly marking pericentromeric heterochromatin (but both also marking non pericentromeric chromatin). Both marks (H3K9me2 and H3K9me3) seemed to be retained in MII oocytes, with some decrease observed in bovine (Table 2). Moreover, in bovine as in the mouse (reviewed in (Canovas and Ross 2016)), some extent of H3K9me2 and me3 remodeling was reported from the zygote to the 8 cell-stage embryo (Pichugin et al. 2010; Wu et al. 2011; Santos et al. 2003).Therefore, *KDM4C* higher abundance in bovine oocytes with more compacted chromatin could be associated to an increased requirement for partial demethylation at the MII stage and/or before genome activation, which is in accordance with the expression profile identified by RNA-seq (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/). On the other hand, KDM4C (also known as JMJD2) was dispensable for female fertility and embryo development in a knock-out mouse model (Pedersen et al. 2014). Interestingly, the mRNA levels of *KDM4C* are also increasing as the follicle grows (Fig. 2B), either supporting the progressive shift towards condensed chromatin or the progressive accumulation for later embryonic use as the oocyte gets closer to ovulation

Moreover both RNAseq (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/) and siRNA mediated gene silencing experiments (Golding et al. 2015) supported the idea that *SETDB1* is required during bovine preimplantation development and therefore, higher amounts in GV1-2 could mean increased storage for future use. The slight decrease observed in GV3 is an interesting feature that remains to be studied. In mice, maternal deletion of SETDB1 results in defects in meiotic progression and preimplantation development (Eymery et al. 2016; Kim et al. 2016)

Interestingly *SUV39H1* and *SUV39H2* transcripts, which encode for methyltransferases that specifically trimethylate H3K9 using H3K9me1 as substrate, do not seem to be much affected by chromatin configuration since only *SUV39H1* increased in GV3 (Fig. 2C). However, both transcripts were

significantly affected by follicular size, which could be related to pericentromeric rearrangements occurring in preparation for meiotic resumption in a follicle size-dependent manner.

4.1.4. Transcripts related to histone H3 Lysine 36 methylation (H3K36me)

Some H3K36 methyl transferases and demethylases were significantly affected during chromatin compaction and/or follicular growth, including *KDM2A* (Fig 2A), *SETD3* (Fig 2D), and *SETD2* (3'UTR variants and constitutive; Fig. 2C). However, we were unable to find any reference in the literature on the occurrence of H3K36me during oocyte growth. Therefore it is not possible to predict the significance of these changes based on the analysis of the phenotype. Moreover, with the exception of one study showing an important role for KDM2A during mouse embryonic development (Kawakami et al. 2015), very little is known on the specific role of these enzymes during oocyte and embryonic development. Thus these are interesting new targets for future studies.

4.1.5. Transcripts related to Histone H4 Lysine 20 trimethylation (H4K20me3)

H4K20me3 is considered a repressive mark and hallmark of pericentromeric heterochromatin (together with H3K9me3) (Souza et al. 2009). In the mouse, it is always clearly associated with pericentromeric chromatin during the NSN to SN transition (Table 2). In the present analysis, transcripts of both the constitutive form of the H4K20me3-specific methyl transferase (*SUV420H1*) and one 3'UTR variants were more abundant in GV1-2-3, compared to GV0. Since the global intensity of this mark did not change during chromatin compaction, we can speculate that these transcripts are accumulated for later use during maturation and/or embryonic development according to the RNA-seq profile (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/)

In mice, the combined siRNA-mediated down regulation of Suv420h1 and 2 resulted in attenuation of H4K20me3 and concomitant accumulation of H4K20me, which led to aberrant chromosome alignment on the MII plate, together with impaired polar body I extrusion (Xiong et al. 2013). On the other hand we

cannot exclude that methyltransferase activity may also be required during chromatin compaction for the maintenance of the H4K20me3 state during oocyte differentiation.

As for the possible role in further embryonic development, H3K20me3 was not detected in mouse embryos and that ectopic expression of SUV420H1 at the 1-cell stage increased H3K20me3 mark and impaired subsequent embryo development (Eid et al. 2016). However, since genomic activation occurs at different stages in mouse and bovine, these results do not help us in interpreting the specific role of maternally inherited *SUV420H1*. Moreover, to the best of our knowledge, no data are available on H4K20me3 during bovine preimplantation development. Therefore, the role *of SUV420H1* transcripts in bovine development remains to be fully elucidated by knockdown analysis.

4.1.6. Transcripts related to histone H3 and H4 acetylation

Several changes in histones acetylation occur during oocyte chromatin compaction and subsequent meiotic resumption and maturation (Table 3). Despite this, relatively few transcripts related to histone acetylation/deacetylation activity were found to be significantly affected in our analysis, which might suggest that transcriptional regulation have limited relevance on histone acetylation processes at this stage, while other translational or post-translational regulatory mechanisms could have major roles.

We have assessed the levels of Histone H4 Lysine 12 and 5 acetylation (H4K12ac and H4K5ac) in cow oocytes. Overall, we observed an increased acetylation level of both K residues during chromatin compaction from GV0 to GV3 oocytes, and a de-acetylation following *in vitro* maturation (Fig. 3). However, acetylation of H4K12 and H4K5 seems to be stage dependent during oogenesis since H4K12ac occured earlier than H4K5ac. As shown in Fig. 2G**,** transcripts for histone acetyltransferase 1 **(***HAT1***)**, which encode protein that acetylates soluble (but not nucleosomal) H4K5 and H4K12, were slightly decreased in GV1-2-3 compared to GV0 oocyte. Moreover, both RNA-seq analysis (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/) and quantitative PCR using oligo-dT (McGraw 2002) detected relatively low levels of *HAT1* transcripts in *in vitro* matured MII oocytes and up to the blastocyst stage when its

468 expression increased. Therefore the reduced amounts in GV 1-2-3 could be associated with translation,
469 which would somehow contribute to increased H4K12ac and H4K5ac during chromatin compaction,
470 followed by transcript degradation.
471
472 Other interesting targets identified by the present analysis were several members of the MYST histone
473 acetylase family. The levels of some transcripts of the MYST group were slightly affected by the
474 chromatin status and/or the follicular size (Fig. 2G and 2H**)**. However, since the precise histone residue
475 target for each of the MYST enzymes has not yet been reported, it is difficult to match the
476 increased/decreased mRNA levels in our contrasts with the observed phenotype (Table 3). Nevertheless,
477 among the MYST transcripts *MYST4* is probably the most promising. Although *MYST4* mRNAs are
478 ubiquitous, immunohistochemistry performed on bovine ovarian sections and whole mount samples,
479 revealed that the MYST4 protein is present in oocytes and in the cytoplasm and nuclei of *in vitro*
480 produced embryos. (McGraw et al. 2007). Moreover, the MYST4 protein accumulated in the GV of
481 oocytes, and then concentrated in the vicinity of the meiotic spindle rather than on chromosomes when
482 oocytes reached the MII stage. Given the global histone deacetylation in *in vitro* matured MII oocytes, it
483 appears unlikely that MYST4 acetylates histones H3 and H4. However, a careful observation of
484 immunofluorescent images of published studies in several species revealed that, although there is a
485 general reduction of most acetylation marks, low levels of acetylation of some K residues were
486 maintained in MII chromosomes (see for example MII stage of Fig. 3A), and this could depend on the
487 species and on the culture procedure. In horse for example, H4K16 was de-acetylated in chromosomes of
488 *in vitro* matured oocytes, while acetylation was retained in *in vivo* matured oocytes (Franciosi et al. 2012;
489 Franciosi et al. 2015). So we cannot exclude that some processes responsible for the maintenance of
490 histone acetylation marks may still function during oocyte maturation. This could explain why not all of
491 the transcripts for members of the MYST family are changing in the same direction.
492

As for the Histone Deacetylase (HDAC) family, as shown in Fig 2I and 2L, the levels of *HDAC2*, *HDAC6*, and *HDAC8* transcripts were significantly affected by the chromatin status and the follicular size. However, since the precise histone residue targets for these enzymes have not been reported yet, it is difficult to match the increased/decreased mRNA levels with the observed phenotype.

4.2. Transcripts encoding histones mRNA

Histone mRNAs are particularly interesting in oocytes since histone isoforms (lately referred to as 'variants') are recognized as key players for chromatin function and are emerging as essential participants in mammalian development (Biterge and Schneider 2014; Maze et al. 2014). However, proper interpretation of histone mRNA level changes in oocytes is not an easy task and the warnings made above for histone modifier enzymes are even more relevant. We know indeed, that histone transcripts are to be stored for the sperm nucleosome formation and for the first few cell divisions, which means that an increased level of the mRNA is not related to immediate translation. Moreover, taking into consideration data available in human and mouse for histones transcripts whose genes are present in clusters (*HIST1*, *HIST2*, and *HIST3* cluster genes), and are typically not poly-adenylated, (Marzluff et al. 2002; Marzluff et al. 2008), we are limited to the ones that have a sufficient polyA stretch to generate an amplified product as previously discussed (Labrecque et al. 2015a). Other histone transcripts might be present but invisible to our analysis. On the other hand, some histone variant mRNAs that are encoded by genes outside the canonical gene clusters are usually polyadenylated (Marzluff et al. 2002; Marzluff et al. 2008). Moreover, in mammalian somatic cells, histones can be further divided into replication-dependent and replication-independent histones: histone genes that are clustered (transcripts are not poly-adenylated) are typically expressed during the S-phase and incorporated into chromatin in a DNA replication-dependent manner, while the others (transcripts are poly-adenylated) are expressed throughout the cell cycle and incorporated into chromatin in a replication-independent manner (Marzluff et al. 2002; Marzluff et al. 2008).

519 Nevertheless, for the purpose of this review, we are currently limited by the still incomplete annotations
520 for the histone related genes in the bovine genome, by the lack of a consolidated unified nomenclature in
521 the literature (Talbert et al. 2012), as well as by the scarcity of information on the pattern of nucleosome
522 composition during oogenesis in mammals and particularly in bovine. For these reasons, a tentative match
523 between changes of histone mRNA levels and relative phenotype is not possible. Therefore, discussion of
524 changes in mRNA encoding for histone proteins will be mostly descriptive. Wherever possible, some
525 hypothesis (sometime provocative) based on data presented in the literature, are also presented; however,
526 as for the discussion presented in the previous paragraphs, we are aware that all of the hypothesis
527 presented here await appropriate validation. Changes of histone transcript levels are presented in Fig. 4
528 and organized according to gene family.
529
530 **4.2.1. Histone cluster 1 and 2 family (HIST1H and HIST2H) transcripts**
531 As shown in Fig 4A, the RNA levels of HIST1H family increase with the shift from GV0 to GV1-2-3. For
532 the HIST2H family, the *HIST2H2AB* mRNA accumulates in a chromatin configuration dependent manner,
533 while the constitutive and the 3'UTR isoform of *HIST2H2BE* accumulate in relation to follicular growth,
534 and *HIST2H3A* accumulates in both conditions.
535
536 Interestingly, a previous study have identified the Activating Transcription Factor-2 transcript (ATF-2),
537 which is recognized as an histone acetyl transferase (Kawasaki et al. 2000), as an important quality factor
538 in cleaving bovine bovine embryos (Orozco-Lucero et al. 2014); moreover *ATF-2* is translated during
539 bovine oocyte maturation (Gohin et al. 2014). EmbyoGene dataset shows that the *ATF-2* constitutive
540 transcript is significantly accumulating in oocytes from larger follicle size and in GV1 and 2 stage oocytes
541 while decreasing in GV3 (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/). This enzyme interacts with H2B
542 (Bruhat et al. 2007) and in our analysis some genes encoding H2B, such as *HIST1H2BA*, *HIST1H2BN* and
543 *HIST2H2BE* transcripts mostly follow the same trend (Fig 4A and 4B). This combination could create a
544 more open context for DNA demethylation to occur, although no one has tested such hypothesis yet.

4.2.2 H2A histone family transcripts

Changes in mRNA levels encoded by the H2A histone family genes are shown in Fig. 4C and 4D. In humans these genes are found outside the principal Histone clusters (Marzluff et al. 2002; Marzluff et al. 2008), so it is not surprising that these mRNAs could be detected in our microarray experiments, as they should all be polyadenylated.

In particular, *H2AFJ* represents a replication independent histone with a polyA tail (Nishida et al. 2005) and its level is high both in the more condensed chromatin and the larger follicles (Fig 4C and 4D). For *H2AFZ*, we have used this gene as a stable gene reference in oocyte since it varies according to transcription capacity and it is polyadenylated (Vigneault et al. 2007); accordingly it is significantly lower in GV1-GV2 and GV3 oocytes when compared to the transcriptionally highly active GV0 oocytes, but it does not change significantly (and is very stable) according to follicular size (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/cgi-bin/DoProfile.cgi?gene=H2AFZ&tissue=oocyte). *H2AFV*, which levels in our analysis change significantly according to chromatin compaction (and the splicing variant to both chromatin configuration and follicle size), is involved in DNA repair. Indeed, in Drosophila, both Ataxia Telangiectasia–Mutated (ATM) and Ataxia Telangiectasia–Related (ATR) kinases phosphorylate H2AV (γ-H2AV), and, using this as a reporter for ATM/ATR activity, Joyce et al. (2011) found that γ-H2AV is continuously exchanged, requiring new phosphorylation at the break site until repair is completed (Joyce et al. 2011). Thus, they conclude that ATM is primarily required for the meiotic Double strand Breaks (DSB) repair response, which includes functions in DNA damage repair and negative feedback control over the level of programmed DSBs during meiosis (Joyce et al. 2011)

To the best of our knowledge, still little is known about the function of each of the H2A protein variants in mammalian oocytes and only recently they are starting to be studied. For example, some immunolocalization survey to detect their presence and localization changes during oogenesis and early embryonic development has been conducted (Wu et al. 2014). Interestingly, the above-mentioned H2AZ

protein (H2AFZ in our dataset**)** was found in growing mouse oocytes (from 1 to 15 day old mice) but not associated with the chromatin (it localizes in the cytoplasm). Then, H2AZ seems to be incorporated in the chromatin after priming of 28 old mice and stays in the chromatin during GVBD and MII. It is then absent from the nuclei of early embryos (from zygotes to morula) and then present in the nuclei of blastocyst (Wu et al. 2014). Moreover, H2AZ null mouse could not be generated since all the embryos died at day 7 post-coitum (Faast et al. 2001). Up to that stage embryo development looked normal, meaning a possible contribution of maternal H2AZ (Faast et al. 2001; Binda et al. 2013; Wu et al. 2014). In bovine, both RNA-seq (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/) and qRT-PCR with both random examers and oligo-dT (Vigneault et al. 2007) detected very low level of *H2AZ* transcript up to genome activation, excluding its possible involvement as a maternal transcript. However we cannot exclude that the maternal H2AZ protein could serve the role. Notably, SETD6 is responsible for H2AZ mono-methylation (Binda et al. 2013). As shown in Fig. 2C the level of a *SETD6* transcript's level is significantly affected by chromatin configuration changes, raising the hypothesis that H2AZ protein could be subjected to regulatory post translational modification in preparation for embryonic development. However, we are aware that this hypothesis still needs to be tested.

4.2.3 H3 Histone family transcripts.

For the transcripts encoded by the histone H3 family, some components show higher levels in the GV 1-2-3 groups compared to GV 0 (see Fig. 4E and 4F) as well as in oocytes from larger follicles compared to the <3mm ones. Among these, *H3F3A* and *H3F3B* are particularly interesting. According to the current annotation, as in mouse (Wen et al. 2014), they both encode for the H3.3 protein. In our analysis the levels of these transcripts changes significantly according to chromatin configuration and/or follicle size **(**Fig. 4E and 4F**)**. Moreover previous data have shown that *H3F3A*, is also associated with a long polyA tail and possess 3'UTR sequences associated with recruitment during oocyte maturation (Gohin et al. 2014). These transcripts and the encoded H3.3 protein could have a similar role to the one documented in the mouse.

In the mouse, indeed, different groups have demonstrated the importance of the histone variant H3.3 for chromatin reprogramming upon fertilization (Akiyama et al. 2011; Lin et al. 2013). In 2011, Akiyama and coworkers, have shown that following fertilization H3.3 is removed from the mouse female pronucleus, suggesting that the epigenetic marks carried by H3.3 in oocytes are erased, thus suggesting that this process might participate in generating totipotency in early embryos (Akiyama et al. 2011). The same group also studied the distribution of H3.2, which is incorporated into the transcriptionally silent heterochromatin, whereas H3.1 and H3.3 occupy unusual heterochromatic and euchromatin locations, respectively (Akiyama et al. 2011). More recently, using both morpholino mediated H3.3 Knockdown in fully grown oocytes and genetic KO of the H3.3 chaperones Hira, Lin and coworkers have shown that Hira-mediated H3.3 incorporation is essential for parental genome reprogramming at fertilization (Lin et al. 2014). In another study, H3.3 siRNA mediated-knockdown in mouse MII oocytes compromised reprogramming and resulted in down-regulation of key pluripotency genes; moreover maternally derived H3.3, and not H3.2 in the donor nucleus, was found to be essential for reprogramming of somatic cell nucleus (Wen et al. 2014).

Importantly, the depletion of the H3.3 chaperone Hira in developing mouse oocytes, and the consequent lack of continuous H3.3/H4 deposition, alters chromatin structure, increases DNase I sensitivity and the accumulation of DNA damage, disrupts gene expression, leads to inefficient de novo DNA methylation and a severe fertility phenotype, thus unequivocally showing the importance of H3.3 continuous histone replacement for transcriptional regulation and normal developmental progression during oogenesis (Nashun et al. 2015). However, precise role of H3.3 protein and encoding mRNA change level still need to be confirmed in bovine.

Changes of the other transcripts encoded by the H3 Histone family, such as *H3F3C*, which rises with follicular size (Fig. 4F) awaits an interpretation. Interestingly, though, *SMYD3* (SET and MYND domain containing 3) is present in slightly higher levels in GV1-2-3 oocytes and the encoded protein interacts with

623 H3F3C
624 (http://www.signalinggateway.org/molecule/query;jsessionid=d784ecaea9b654d77c593e053f32a7d52deb
625 33c61364f64af4b5ff6d40c7a0b9?afcsid=A006027&type=interactioninfo&adv=latest&idx=26400349),
626 whose mRNA is accumulated in a follicular size dependent manner. Here again, one could speculate that
627 the uptake and acetylation of H3F3C could be associated with the preparation for DNA access associated
628 with post-fertilization reprogramming. We are aware that all these interesting finding must be validated by
629 specific KO experiment to validate the roles proposed by their expression patterns.
630
631 **4.2.4 H1 histone family transcripts**
632 For the linker histones H1 family, the mRNA of the somatic form (*H1F0*) surprisingly goes up in the GV3
633 stage, while *H1FOO*, which so far is the only oocyte-specific H1 histone variant is accumulated during
634 chromatin compaction; only *H1FOO* mRNA level is affected by follicular size (Fig. 4G and 4H).
635 Interestingly we have found a 3 'UTR sequence in the *H1FOO* that promotes translation during
636 maturation and accordingly a longer polyA tail for this transcript between GV and MII (Gohin et al. 2014).
637 Further possible significances of H1 histone family changes have been already discussed in our previous
638 publications (Labrecque et al. 2015a).
639
640 **5. Conclusions**
641
642 In the last decade, the availability of 'omics' technologies (mainly microarray- and RNAseq- based
643 transcriptomic platforms) applicable to scarce samples such as oocytes, generated a large amount of data.
644 However, these information are difficult to interpret not only for the limits imposed by the technical
645 inaccurateness of protein determination in such samples, which precludes appropriate validation, but also
646 for the peculiar physiology of the oocyte. Assessment of epigenetic modifications and in particular the
647 histone related ones, is even more difficult. In fact, it is becoming more and more clear that oocytes escape

common rules of the 'Histone Code' that applies to somatic cells (Jenuwein and Allis 2001; Suganuma and Workman 2011)

We have tried to overcome the present limitations by integrating data coming from different microarray analysis and critically combining changes of mRNA levels with the corresponding phenotype as well as changes occurring in the early embryo, which in turn enable the formulation of precise hypotheses. We believe that this approach could reveal the function of specific enzymes in the oocyte. In turn these information will be useful in future studies, in which the experimental disruption of these enzyme would finally reveal the biological significance of the corresponding histone modification. Clearly the ambitious goal would be deciphering of the oocyte-specific histone code. Finally, this approach could be particularly useful in large mammalian species, including humans, that most of the times do not allow the application of sophisticated genetic manipulation for the confirmation of experimental hypothesis.

663

664 **References**

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983

984 **Figures legend**

985

986 **Figure 1**

987 **Graphic representation of chromatin compaction in the oocyte nucleus (Germinal Vesicle, GV),**
988 **occurring during meiotic arrest at the diplotene stage**. Morphologically, the chromosomes seem to
989 loose their individuality forming a loose chromatin mass, which in turn undergoes profound and dynamic
990 rearrangements within the GV before the meiotic resumption. Although different terminology has been
991 used in different mammals, chromatin compaction is a common process in which the oocyte chromatin
992 condenses and rearranges progressively passing through intermediate configurations. In mouse, the
993 chromatin is initially found dispersed throughout the nucleoplasm and appears mainly decondensed in a
994 configuration termed 'Non Surrounded Nucleolus' (NSN). Thereafter, chromatin condensation increases,
995 and few chromatin foci start to associate with the nucleolar periphery until a complete rim of
996 heterochromatin is formed in close apposition with the nucleolus (Surrounded Nucleolus, SN
997 configuration), Notably, NSN type configuration is typical of oocytes collected from primordial to
998 growing preantral follicles; nonetheless, NSN oocytes are also found in antral follicles that indeed enclose
999 both NSN and SN oocytes; the origin of the oocyte should always be carefully considered when studying
1000 mouse oocytes with NSN chromatin configuration (Mattson and Albertini 1990; Zuccotti et al. 1995;
1001 Bouniol-Baly et al. 1999). In cow, the oocytes with uncondensed chromatin (GV0 oocytes) are typically
1002 found in early antral follicles (0.5-2 mm), while they are absent in larger follicles. In contrast, oocytes
1003 with increasing levels of compaction (GV1, GV2 and GV3) are collected from medium antral follicle (2-8
1004 mm diameter) (Lodde et al. 2007) and their distribution does not depend on follicular size within this
1005 category (see text) (Dieci et al. 2016). In post-pubertal pig, oocytes with uncondensed chromatin (termed
1006 'Filamentous Chromatin', FC configuration) represent the majority of oocytes collected from early antral
1007 follicle (0.5.2 mm), while oocytes with intermediate (Stringy Chromatin, SC configuration) and high level

of compaction (GV1 configuration) are distributed in medium antral follicles (3-6 mm) (Dieci et al. 2013; Bui et al. 2007). Modified from (Luciano and Lodde 2013).

Figure 2

Changes of mRNAs encoding for histone remodelling enzymes according to chromatin configuration (left panel) and follicular growth (right panel). The data represent the profiles in the original microarray analysis, and are obtained/imported from the EmbyoGENE profiler web site (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/)

Figure 3

Representative images showing H4K12 (A) and H4K5 (B) acetylation in GV0, GV1, GV2, GV3 and MII bovine oocytes. H4K12ac and H4K5ac levels were analyzed by indirect immunofluorescence using polyclonal anti-AcH4K12 or anti-AcH4K5 antibodies (Upstate Biotechnologies, Inc., Lake Placid, NY, USA) and subsequent confocal microscopy. A total of 100 GV and 35 MII stage oocytes were analyzed. Fluorescence intensities were arbitrarily classified as absent, weak or intense. H4K12 was highly acetylated in all the GV1, GV2 and GV3 oocytes and in 46.1% of GV0 oocytes, while the remaining 53.9% of GV0 oocytes showed none or weak H4K12 acetylation signal. H4K5 was absent in all the GV0 and in 20% of GV1 oocytes. 20% of GV1 oocytes were weakly acetylated, while the remaining 60% were highly acetylated. Roughly half of the GV2 and GV3 oocytes were weakly acetylated and the other half showed intense acetylation signals. All the images are the three-dimensional confocal reconstructions of each sample.

Figure 4

Changes of mRNAs encoding for histone proteins according to chromatin configuration (left panel) and follicular growth (right panel). The data represent the profiles in the original microarray analysis,

and are obtained/imported from the EmbyoGENE profiler web site (http://emb-bioinfo.fsaa.ulaval.ca/IMAGE/)

Tables

Table 1:

Possible significances of mRNA level changes in oocytes

Table 2:

Overview of histones H3 and H4 methylation during chromatin compaction and meiotic maturation in mammals.

Data available in the literature have been critically revised to build an overview of patterns of H3 and H4 methylation within and across species. **Uncondensed** category includes: NSN configuration in mouse (NOTE that only data of NSN collected from antral follicles are reported, for data on early growing NSN please refer to the specific reference); GV0 in cow, F in pig. **Intermediate** category includes: pNSN and pSN in mouse; GV1 and GV2 in cow; SC in pig. **Condensed** configuration includes SN in mouse; GV3 in cow; GV1 in pig. **p-Ch**: pericentromeric Chromatin; **c-Ch**: centromeric Chromatin; **r-Ch**: rest of the Chromatin; **na**: not assessed; (+): present; (+/): weak; **(-)** : absent; (**?**): discordant data in the literature within the same species.

Table 3:

Overview of histones H3 and H4 acetylation during chromatin compaction and meiotic maturation in mammals.

Data available in the literature have been critically revised to build an overview of histones H3 and H4 acetylation within and across species. **Uncondensed** category includes: NSN configuration in mouse (NOTE that only data of NSN collected from antral follicles are reported, For data on early growing NSN

please refer to the specific reference); GV0 in cow, F in pig. **Intermediate** category includes: pNSN and pSN in mouse; GV1 and GV2 in cow; SC in pig. **Condensed** configuration includes SN in mouse; GV3 in cow; GV1 in pig. **p-Ch**: pericentromeric Chromatin; **c-Ch**: centromeric Chromatin; **r-Ch**: rest of the Chromatin; **na**: not assessed; (+): present; (+/): weak; **(-)** : absent; (**?**): discordant data in the literature within the same species.

Supplemental table 1

List of the 4340 targets identified by the meta-analysis as affected by the combination of chromatin status and follicular size

Table 1:

Change of transcript level assessed during chromatin compaction	Meaning
Decrease	- Less transcription - Shortening of poly A tail and storage for future use - Degradation - Translation and subsequent degradation
Increase	- More transcription for storage for future use - More transcription for protein that are required at the time

6 **Table 2:**

Modification	Species	Uncondensed	Intermediate		Compacted	Fully Grown	MII (in vivo/in vitro)	References
H3Arg17me	**Bovine**	na	na	na	na	na	na / na	(Sarmento et al. 2004)
	Mouse	na	na		na	+	- / na	
	Porcine	na	na		na	na	na / na	
H3Argme3	**Bovine**	na	**na**	**na**	na	na	na /na	(Sarmento et al. 2004)
	Mouse	na	na		na	+	- / na	
	Porcine	na	na		na	na	na / na	
H3K27me1	**Bovine**	na	na	na	na	na	na / na	(Park et al. 2009)
	Mouse	na	na		na	na	na / na	
	Porcine	na	na		na	+	na / +	
H3K27me3	**Bovine**	na	na	na	na	++	na / +/-	(Bonnet-Garnier et al. 2012; Ross et al. 2008; Park et al. 2009)
	Mouse	- (p-Ch); + (c-Ch & r-Ch)	+/- (p-Ch); + (cc-Ch & r-Ch)		+/- (p-Ch); + (c-Ch & r-Ch)	+	na / na	
	Porcine	na	na		na	+	na / +	
H3K4me2	**Bovine**	na	na	na	na	na	na /na	(Kageyama et al. 2007; Lin et al. 2016)
	Mouse	+	+		++	+	na /na	
	Porcine	na	na		na	na	na / na	
H3K4me3	**Bovine**	na	na	na	na	na	na /na	(Kageyama et al. 2007; Bonnet-Garnier et al. 2012; Fulka 2008)
	Mouse	+ (excl. from p-Ch & c-Ch)	+ (excl. from p-Ch & c-Ch)		++ (excl. from p-Ch & c-Ch)	+	+ / na	
	Porcine	na	na		na	na	na /na	
H3K9me1	**Bovine**	na	na	na	na	+	na / +	(Wee et al. 2010)
	Mouse	na	na		na	na	na / na	
	Porcine	na	na		na	na	na / na	
H3K9me2	**Bovine**	na	na	na	na	+	na / +	(Kageyama et al. 2007; Meglicki et al. 2008; Lin et al. 2016; Wee et al. 2010; Racedo et al. 2009; Bui et al. 2007)
	Mouse	+ (pCh & r-Ch)	+ (p-Ch & r-Ch)		++ (p-Ch and r-Ch)	+	na / +	
	Porcine	na	na		na	na	na / na	
H3K9me3	**Bovine**	na	na	na	na	+	na / +/-	(Kageyama et al. 2007; Endo et al. 2005; Meglicki et al. 2008; Bonnet-Garnier et al. 2012; Zhang et al. 2016b; Wee et al. 2010; Bui et al. 2007; Russo et al. 2013)
	Mouse	+ (higher in p-Ch)	+ (higher in p-Ch)		+ (higher in p-Ch)	+	na / +	
	Porcine	+/-	+		+	+	na / +	
	Sheep	+	na		+	na	na / na	
H4K20me3	**Bovine**	na	na	na	na	na	na /na	(Bonnet-Garnier et al. 2012)
	Mouse	+ (p-Ch only)	+ (p-Ch only)		+ (p-Ch only)	+	+ / na	
	Porcine	na	na		na	na	na / na	

7

Table 3

Modification	Species	Uncondensed	Intermediate		Compacted	Fully Grown	MII (in vivo/in vitro)	References
H3K14ac	**Bovine**	na	na	na	na	+	na / +/-	(Meglicki et al. 2008; Lin et al. 2016; Wang et al. 2006; Wang et al. 2011; Bui et al. 2007)
	Mouse	+ (excl. from p-Ch)	+ (excl. from p-Ch)		++ (excl. from p-Ch)	+	na / -	
	Porcine	+	+		+	+	na / ?	
H3K18ac	**Bovine**	na	na	na	na	na	na / na	(Kageyama et al. 2007; Bui et al. 2007)
	Mouse	na	na		na	+	na / na	
	Porcine	+	+		+	+	na / -	
H3K4ac	**Bovine**	na	na		na	na	na / na	(Endo et al. 2005)
	Mouse	na	na		na	na	na / na	
	Porcine	na	na		na	+	na / -	
H3K9,K1ac	**Bovine**	na	na		na	na	na / na	(Nagashima et al. 2007; Meglicki et al. 2008)
	Mouse	+ (excl. from p-Ch)	+ (excl. from p-Ch)		+ (excl. from p-Ch)	+	na / -	
	Porcine	na	na		na	na	na / na	
H3K9ac	**Bovine**	na	na	na	na	+	na / -	(Kageyama et al. 2007; Endo et al. 2005; Fulka 2008; Wang et al. 2006; Wee et al. 2010; Bui et al. 2007)
	Mouse	na	na		na	+	- /na	
	Porcine	+	na		+	+	na / -	
H4hyperac	**Bovine**	na	na	na	na	na	na / na	(Sarmento et al. 2004; Fulka 2008)
	Mouse	na	na		na	+	- / na	
	Porcine	na	na		na	na	na / na	
H4K12ac	**Bovine**	+/-	+	+	+	+	na / -	This paper; (Kageyama et al. 2007; Kim et al. 2003; Akiyama et al. 2006; Endo et al. 2005; Maalouf et al. 2008; Lin et al. 2016; Franciosi et al. 2012; Fulka 2008; Wang et al. 2006; Racedo et al. 2009)
	Mouse	+	+		++	++	- / -	
	Porcine	na	na		na	+	na / ?	
	Horse	+++	++		+	+	- / -	
H4K16ac	**Bovine**	na	na	na	na	+	na / -	(Kim et al. 2003; Akiyama et al. 2006; Maalouf et al. 2008; Lin et al. 2016; Franciosi et al. 2012; Wang et al. 2006)
	Mouse	+	+		++	+	- / -	
	Porcine	na	na		na	+	na / -	
	Horse	+	+		++	+*	+ / -	
H4K5ac	**Bovine**	-	+/-	+	+	+	na / -	This paper; (Kageyama et al. 2007; Kim et al. 2003; Nagashima et al. 2007; Endo et al. 2005; Maalouf et al. 2008; Bonnet-Garnier et al. 2012; Wang et al. 2006; Wee et al. 2010)
	Mouse	+ (excl. from p-Ch & c-Ch)	++ (excl. from p-Ch & c-Ch)		++ (excl. from p-Ch & c-Ch)	++	na / -	
	Porcine	na	na		na	+	na / -	
H4K8ac	**Bovine**	na	na	na	na	+	na / +/-	(Kim et al. 2003; Akiyama et al. 2006; Endo et al. 2005; Maalouf et al. 2008; Franciosi et al. 2012; Wang et al. 2006)
	Mouse	na	na		na	+	+/- / +/-	
	Porcine	na	na		na	na	na / ?	
	Horse	+++	++		+	+	- / -	

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FIGURE 1

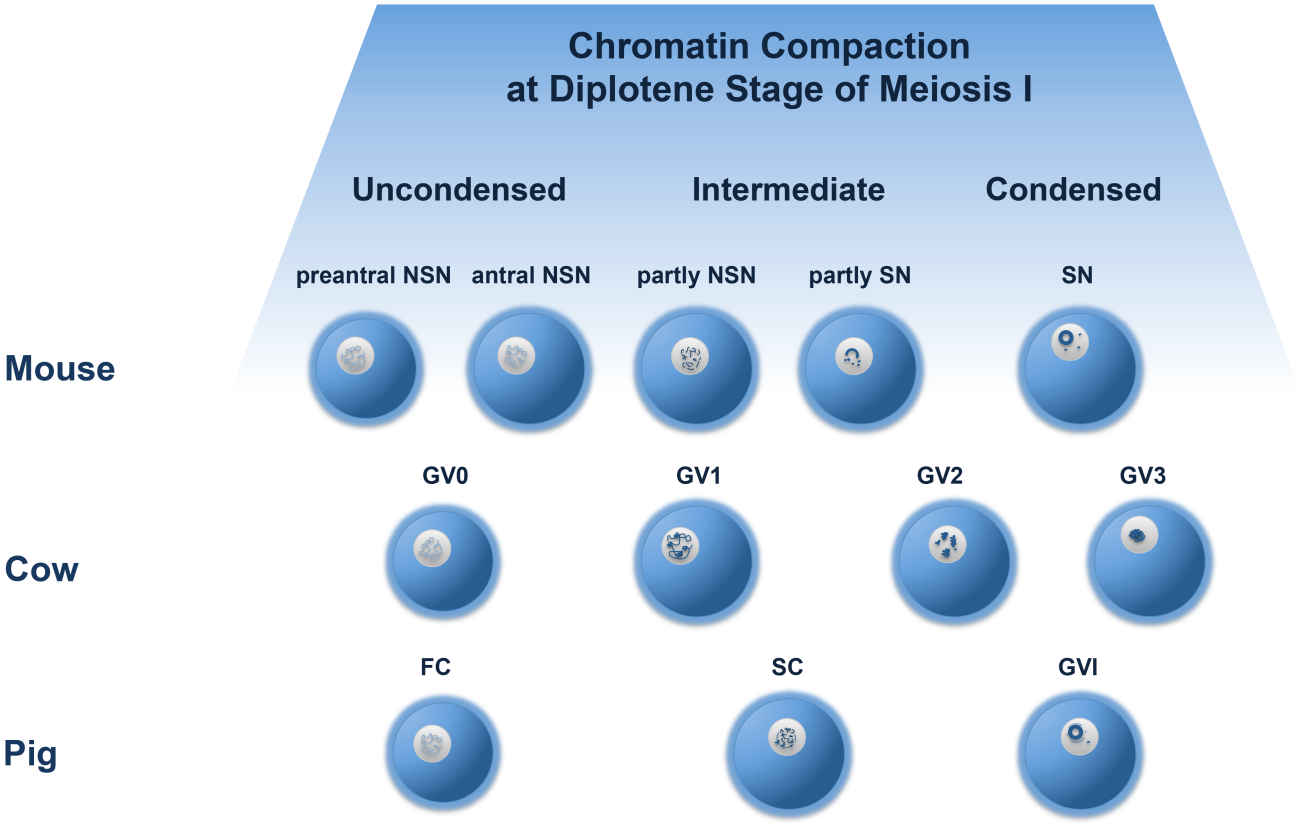

Chromatin Compaction
at Diplotene Stage of Meiosis I
Uncondensed
Intermediate
Condensed
preantral NSN
antral NSN
partly NSN
partly SN
SN
Mouse
GV0
GV1
GV2
GV3
Cow
FC
SC
GVI
Pig

FIGURE 2

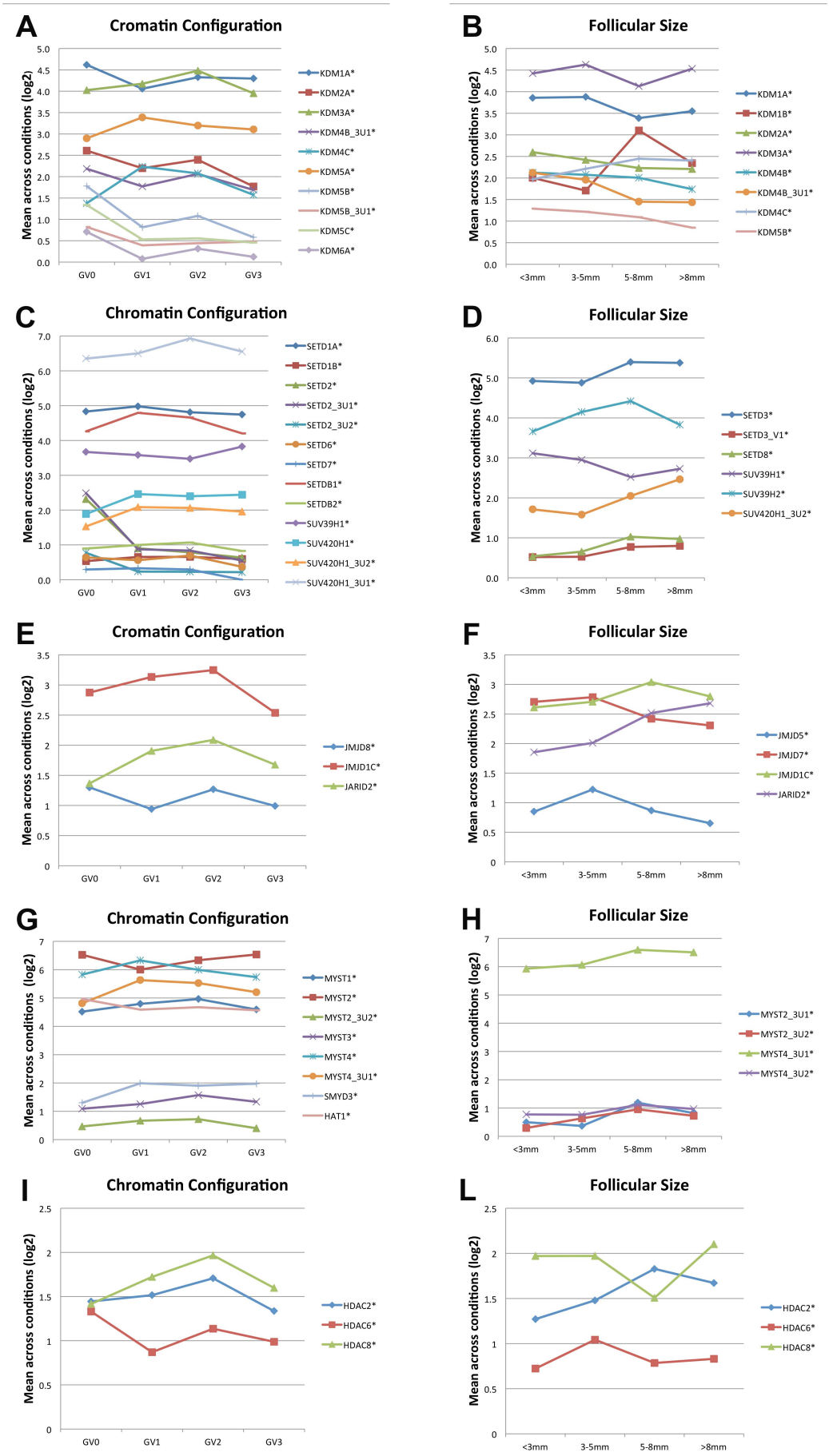

A
Cromatin Configuration
Mean across conditions (log2)
GV0
GV1
GV2
GV3
KDM1A*
KDM2A*
KDM3A*
KDM4B_3U1*
KDM4C*
KDM5A*
KDM5B*
KDM5B_3U1*
KDM5C*
KDM6A*
B
Follicular Size
<3mm
3-5mm
5-8mm
>8mm
KDM1A*
KDM1B*
KDM2A*
KDM3A*
KDM4B*
KDM4B_3U1*
KDM4C*
KDM5B*
C
Chromatin Configuration
SETD1A*
SETD1B*
SETD2*
SETD2_3U1*
SETD2_3U2*
SETD6*
SETD7*
SETDB1*
SETDB2*
SUV39H1*
SUV420H1*
SUV420H1_3U2*
SUV420H1_3U1*
D
Follicular Size
SETD3*
SETD3_V1*
SETD8*
SUV39H1*
SUV39H2*
SUV420H1_3U2*
E
Cromatin Configuration
JMJD8*
JMJD1C*
JARID2*
F
Follicular Size
JMJD5*
JMJD7*
JMJD1C*
JARID2*
G
Chromatin Configuration
MYST1*
MYST2*
MYST2_3U2*
MYST3*
MYST4*
MYST4_3U1*
SMYD3*
HAT1*
H
Follicular Size
MYST2_3U1*
MYST2_3U2*
MYST4_3U1*
MYST4_3U2*
I
Chromatin Configuration
HDAC2*
HDAC6*
HDAC8*
L
Follicular Size
HDAC2*
HDAC6*
HDAC8*

FIGURE 3

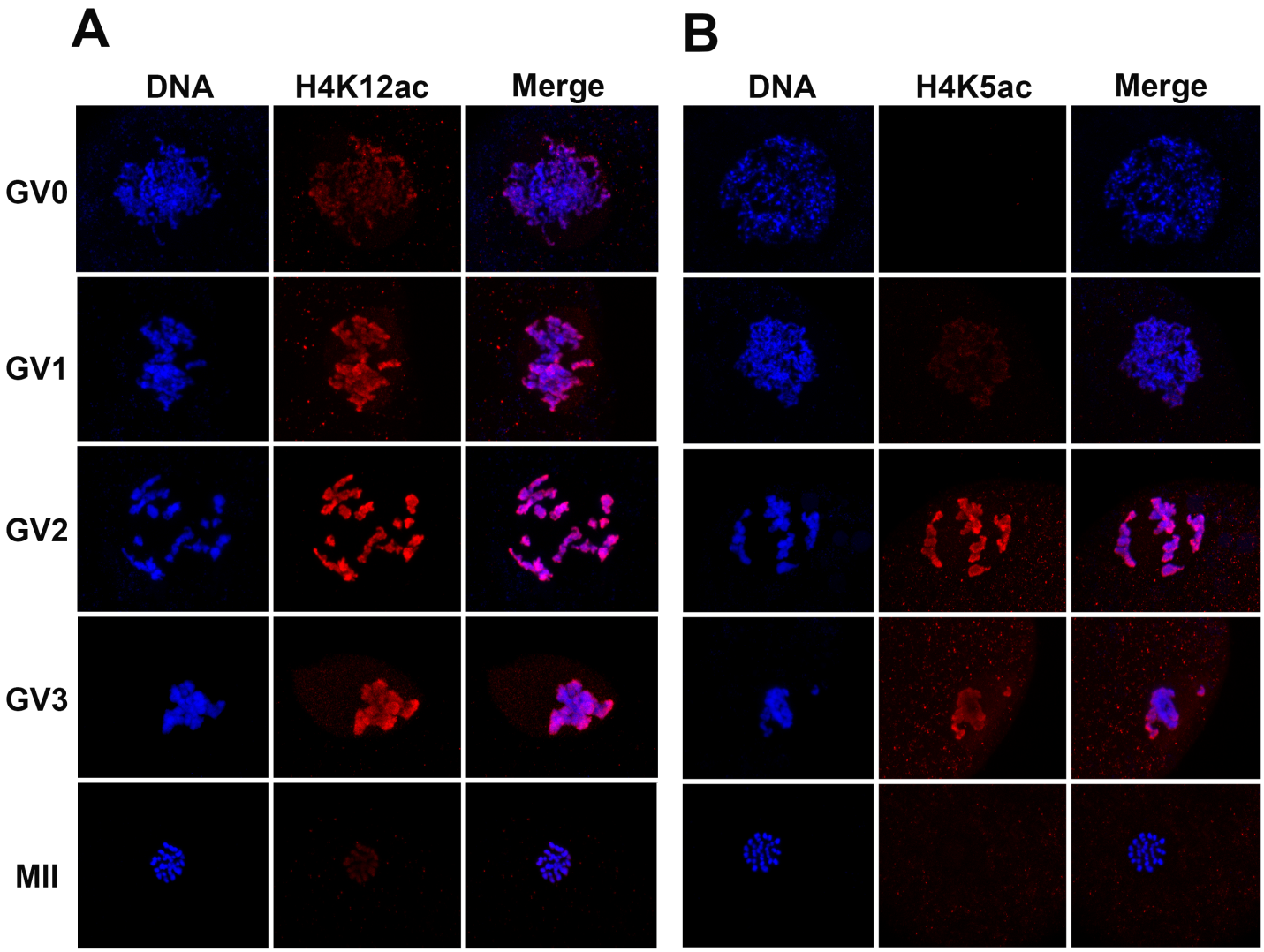
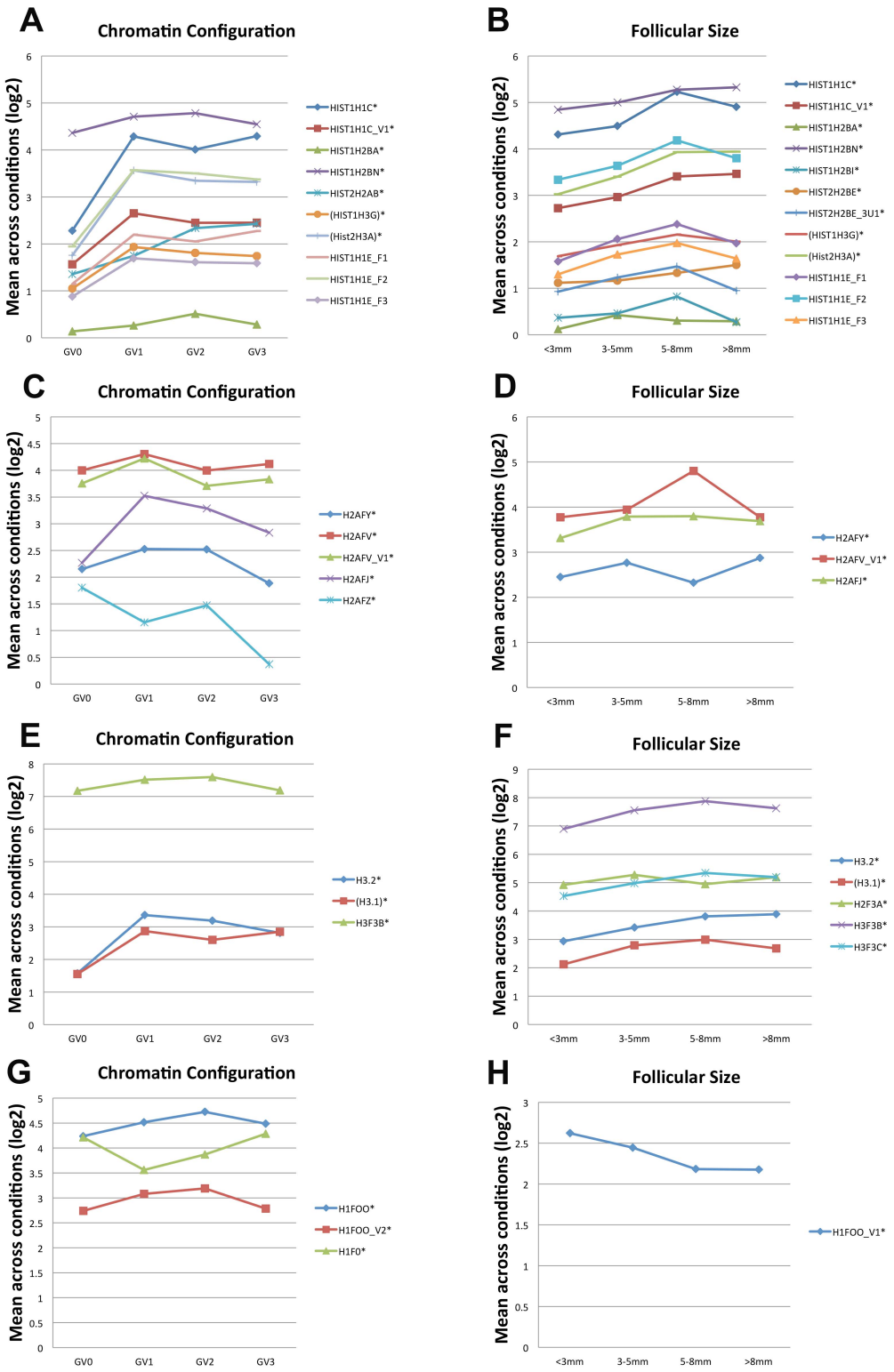


FIGURE 4


A
Chromatin Configuration
Mean across conditions (log2)
GV0
GV1
GV2
GV3
HIST1H1C*
HIST1H1C_V1*
HIST1H2BA*
HIST1H2BN*
HIST2H2AB*
(HIST1H3G)*
(Hist2H3A)*
HIST1H1E_F1
HIST1H1E_F2
HIST1H1E_F3
B
Follicular Size
<3mm
3-5mm
5-8mm
>8mm
HIST1H1C*
HIST1H1C_V1*
HIST1H2BA*
HIST1H2BN*
HIST1H2BI*
HIST2H2BE*
HIST2H2BE_3U1*
(HIST1H3G)*
(Hist2H3A)*
HIST1H1E_F1
HIST1H1E_F2
HIST1H1E_F3
C
Chromatin Configuration
H2AFY*
H2AFV*
H2AFV_V1*
H2AFJ*
H2AFZ*
D
Follicular Size
H2AFY*
H2AFV_V1*
H2AFJ*
E
Chromatin Configuration
H3.2*
(H3.1)*
H3F3B*
F
Follicular Size
H3.2*
(H3.1)*
H2F3A*
H3F3B*
H3F3C*
G
Chromatin Configuration
H1FOO*
H1FOO_V2*
H1F0*
H
Follicular Size
H1FOO_V1*