Other Histone Modifications Dynamics in Early Embryonic Development

Subjects: Genetics & Heredity

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Mammalian fertilization initiates the reprogramming of oocytes and sperm, forming a totipotent zygote. During this intricate process, the zygotic genome undergoes a maternal-to-zygotic transition (MZT) and subsequent zygotic genome activation (ZGA), marking the initiation of transcriptional control and gene expression post-fertilization. Histone modifications are pivotal in shaping cellular identity and gene expression in many mammals.

Keywords: histone modifications ; embryonic development ; zygotic genome activation (ZGA) ; H3K36me3 ; allelic reprogramming ; H3R26me2 ; embryos

1. Introduction

Mammalian fertilization initiates with the fusion of an oocyte and a single sperm, a critical event in which these two terminally differentiated germ cells must undergo reprogramming to establish a totipotent zygote [1][2][3]. While germ cell chromatin is globally transcriptionally silent before fertilization, particularly regarding mRNA transcription, it is noteworthy that several non-coding RNAs (ncRNAs) are nascent expressed, playing critical roles in meiosis and post-fertilization development [4]. The oocyte's meiotic resumption and the early zygote's development rely on stored maternal transcripts until these are gradually degraded. The transition, known as the maternal-to-zygotic transition (MZT) [5][6], involves the meticulous coordination of maternal product clearance with zygotic genome activation (ZGA), marking the initiation of transcriptional control and gene expression post-fertilization [7][8]. As this intricate transformation unfolds, control over developmental processes gradually shifts to the RNAs and proteins newly synthesized in the zygote. It becomes evident that epigenetic modifications are pivotal in orchestrating this fundamental transformation [9]. Subsequently, ZGA is succeeded by the emergence of distinct cell identities within embryonic cells, leading to their differentiation into the inner cell mass (ICM) and trophectoderm (TE) stages at the blastocyst stage [10].

Epigenetic modifications occurring in terminally differentiated gametes, including DNA methylation [11][12][13], histone modifications [14][15][16], chromatin accessibility [17][18][19], and 3D chromatin structures [20][21], can be reset to a foundational state following fertilization. This reset process is crucial for achieving totipotency and supporting the subsequent development of a new individual. The precise regulation of zygotic gene transcription is intricately linked to chromatin accessibility. It underscores the pivotal role of epigenetic information in upholding cellular identity and governing gene expression. The nucleosome, serving as the fundamental unit of chromatin, consists of octamers comprising two copies of the core histone proteins H2A, H2B, H3, and H4 [22][23]. The modulation of chromatin accessibility is mediated via the positioning and configuration of nucleosomes, factors influenced by histone variants, and the post-translational modification of histone N-terminal tails. Several studies have increasingly suggested that histone modifications and variants are pivotal in ensuring precise control over ZGA [24][25][26].

2. H3K36me3 Dynamics Unveiled: Allelic Reprogramming in Early Mouse Embryos

The methylation of H3K36 (H3K36me), a highly conserved process from yeast to humans, is intricately associated with transcribed regions, playing pivotal roles in transcription fidelity [27][28], RNA splicing [29][30] and DNA repair [31][32]. In mammals, SET domain containing 2 (SETD2) emerges as the primary methyltransferase responsible for catalyzing H3K36 trimethylation (H3K36me3) in vivo [33][34][35]. SETD2 facilitates the interaction with RNA polymerase II, orchestrating the coupling of H3K36me3 with transcription elongation [36]. Unlike H3K4me3, H3K36me3 exhibits a positive correlation with DNA methylation, recruiting DNA methyltransferase 3A and 3B (DNMT3A/B) and maintaining this association in various mammalian cells [37][38].

Several studies underscore the critical roles of SETD2 levels and H3K36me3 in establishing and safeguarding the maternal DNA methylome during oogenesis and early embryo development. In mice, SETD2-depleted oocytes experience a significant loss of H3K36me3, leading to invasions of H3K4me3 and H3K27me3 into regions formerly marked by H3K36me3 [39]. Additionally, SETD2-deficient oocytes result in an aberrant DNA methylome characterized by the loss of maternal imprints and anomalous deposition of H3K4me3 instead of DNA methylation, particularly at imprinted control regions (ICRs) [40].

Furthermore, the scarcity of SETD2 has been demonstrated to induce defects in oocyte maturation and embryonic lethality. Mice deficient in SETD2 do not survive beyond embryonic day (E) 10.5–E11.5 [41]. Notably, the overexpression of H3.3K36M (lysine to methionine mutant) in mouse MII oocytes results in reduced H3K36me3 levels and compromised embryo viability [42].

The study of allelic reprogramming of H3K36me3 post-fertilization in early mouse embryos has provided valuable insights. Given the transient inheritance of maternal marks H3K4me3 and H3K27me3, influencing processes like ZGA [43], imprinted X chromosome inactivation [44], and gene expression [45], the inquiry arises regarding the inheritance of H3K36me3 in early embryos and its potential interaction with other epigenetic marks. Recent immunofluorescence studies have uncovered the presence of H3K36me3 at all stages except in paternal pronuclei shortly after fertilization [40]. Analyses of H3K36me3 via ChIP-seq in sperm and discrimination of parental strains via single-nucleotide polymorphisms (SNPs) revealed a significant allelic imbalance in 1-cell embryos, with a notably higher number of maternal reads than paternal reads [46][47]. Surprisingly, H3K36me3 inherited from oocytes appears present in 1-cell embryos but diminishes considerably by the late 2-cell stage and is lost by the 8-cell stage [48]. Conversely, most, if not all, H3K36me3 peaks in sperm are lost in zygotes [49]. The temporal transition of H3K36me3 from parental to zygotic patterns aligns closely with ZGA, suggesting allelic reprogramming during early embryo development [50]. Notably, maternal H3K27me3 persists beyond ZGA in the blastocyst, potentially influencing the deposition of zygotic H3K36me3. Genes with paternal-specific H3K36me3, as opposed to maternal-specific H3K36me3, exhibit a preference for reciprocal allelic H3K27me3. This group includes many H3K27me3-controlled imprinted genes, indicating the occurrence of H3K36me3 in early embryos and its role in marking allele-specific gene expression [39].

3. Histone H3R26me2: Pivotal in Cell Fate Determination in Embryos

After ZGA, embryos undergo multiple cell divisions before the first segregation into cell lineages, giving rise to TE and ICM cells. TE lineage, marked by Cdx2 and Gata3 expression, plays a role in placental development [51][52][53]. In contrast, cells in the ICM, recognized by pluripotent factors, undergo differentiation into epiblast and primitive endoderm, giving rise to all embryonic tissues and certain extraembryonic membranes [54][55][56]. During differentiation, the HIPPO pathway regulates the TE lineage [57][58], and epigenetic modifications consolidate the ICM lineage [59].

Previously explored studies have highlighted the role of Histone 3 Arginine 26 dimethylation (H3R26me2) as a recently identified epigenetic mechanism [60]. This process, predominantly governed by Coactivator-associated arginine methyltransferase 1 (CARM1), has been reported to influence pluripotency in mouse embryos and mESCs [61]. The overexpression of CARM1 in embryonic stem cells (ESC) and early mouse embryos' blastomeres drives an increase in H3R26me2 at pluripotent gene promoters [62][63][64], such as Oct4/Pou5f1 [65], Nanog [66], and Sox2 [67][68]. This epigenetic mark linked to gene activation determines the elevated expression of these genes, closely related to cell fate determination and the pluripotent capacity of these cells.

The asymmetrical distribution of H3R26me2 in blastomeres is detected in embryos as early as the four-cell stage [63]. Blastomeres with higher levels of CARM1 and H3R26me2 contribute more significantly to the formation of the ICM [69]. Furthermore, higher levels of H3R26me2 enhance the expression of pluripotent genes and facilitate Sox2 binding to its targets, contributing to ICM specification. Additionally, CARM1 overexpression can increase the frequency of asymmetric cell divisions, leading cells to adopt a more internal position in the embryo [69]. Alongside CARM1, another chromatin regulator named PR domain-containing 14 (PRDM14) is also asymmetrically expressed in four-cell embryos, thus modulating the level of H3R26me2 to favor contribution to the ICM [70][71][72].

Early cell fate determination in mouse embryos has recently been suggested to commence at the late 2-cell stage [73]. At this point, a long non-coding RNA (lncRNA) known as LincGET is transiently and asymmetrically expressed in the nucleus, extending from the 2-cell to the 4-cell stage [65]. LincGET interacts with CARM1, accumulating it in nuclear granules that require the presence of the Nuclear Paraspeckle Assembly Transcript 1 (NEAT1) and its partner Nuclear RNA-binding protein 54 kDa (P54NRB) [73][74]. It results in a significant increase in the H3R26me2 level, activation of ICM-specific gene expression, positive regulation of transposons, and an increase in global chromatin accessibility. It is

important to note that introducing LincGET into one of the blastomeres of 2-cell embryos can potentially redirect their differentiation toward the ICM [65].

The lncRNA named Neat1 is also required to mark H3R36me2, which is CARM1-dependent and crucial for ICM specification [75]. NEAT1 shows an asymmetrical expression among blastomeres in 4-cell embryos and recruits CARM1 in paraspeckle nuclear foci [50]. Disruption of NEAT1 results in a decrease in H3R26me2, an increase in Cdx2 expression, and a biased specification toward the TE lineage [63][76].

In summary, the asymmetry in the distribution of H3R26me2 emerges as one of the early signals guiding lineage specification. The variability in H3R26me2 is carefully regulated by the asymmetrical expression of CARM1, PRDM14, LincGET, and NEAT1 in the early blastomeres. Although the cause of the initial skewed expression of CARM1/PRDM14/LincGET/NEAT1 in 2-cell and 4-cell embryos is not fully understood, these findings provide a clearer understanding of the molecular events orchestrating cell fate determination in the early stages of embryonic development.

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