# Epigenetic Reprogramming in Early Animal Development

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Dramatic nuclear reorganization occurs during early development to convert terminally differentiated gametes to a totipotent zygote, which then gives rise to an embryo. Aberrant epigenome resetting severely impairs embryo development and even leads to lethality. How the epigenomes are inherited, reprogrammed, and reestablished in this critical developmental period has gradually been unveiled through the rapid development of technologies including ultrasensitive chromatin analysis methods. In this review, we summarize the latest findings on epigenetic reprogramming in gametogenesis and embryogenesis, and how it contributes to gamete maturation and parental-to-zygotic transition. Finally, we highlight the key questions that remain to be answered to fully understand chromatin regulation and nuclear reprogramming in early development.

Gametogenesis and embryogenesis are essential to give rise to a new life and to repopulate species that use sexual reproduction. Sperm and oocytes arise from primordial germ cells (PGCs) through spermatogenesis and oogenesis, respectively. After fertilization, the two terminally differentiated gametes fuse and form a totipotent zygote (Zhou and Dean 2015). During embryo cleavage, maternal proteins and mRNAs are gradually degraded, while the zygotic genome is transcriptionally activated, collectively leading to the maternal-to-zygotic transition (MZT) (Fig. 1; Schultz 2002; Walser and Lipshitz 2011). Zygotic genome activation ([ZGA], also known as embryonic genome activation) often takes place in two waves (for review, see Lee et al. 2014). During minor ZGA in mouse embryos, the transcription of a small subset of genes is accompanied by promiscuous, genome-wide transcription, which occurs from the S phase of a one-cell embryo until the onset of "major ZGA" in mid- to late two-cell embryos, when thousands of genes are activated (Bouniol et al. 1995; Nothias et al. 1996; Aoki et al. 1997; Hamatani et al. 2004; Wang et al. 2004; Zeng et al. 2004; Abe et al. 2015). Concomitantly, RNA polymerase II (Pol II) undergoes dynamic chromatin engagement during the minor-to-major ZGA transition (Bellier et al. 1997; Liu et al. 2020). In human, embryonic transcripts are first observed from the two-cell to the four-cell stage, and the major ZGA occurs around the eight-cell stage (Tesarik et al. 1987; Braude et al. 1988; Dobson et al. 2004). The

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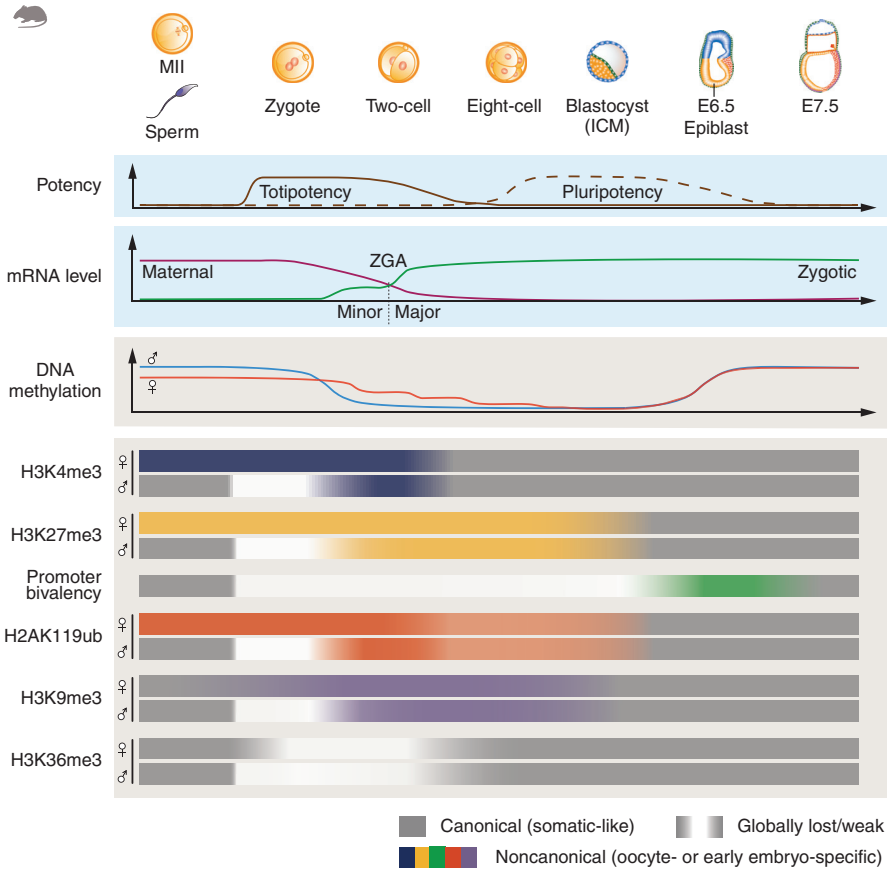


**Figure 1.** Transcription and epigenetic dynamics from gametes to embryos in mouse. After fertilization, the terminally differentiated gametes are converted into a totipotent zygote. Inner cell mass (ICM) cells from blastocysts are pluripotent and can give rise to all embryonic tissues. The accumulated maternal mRNAs undergo degradation after fertilization, while minor and major zygotic genome activation (ZGA) emerge around the one-cell and two-cell stages, respectively. Parental genomes undergo global DNA demethylation starting from the zygote stage and the reestablishment of embryonic DNA methylome occurs in postimplantation embryos. For histone modifications, sperm largely display canonical distributions (similar to somatic cells), while oocytes and early embryos often acquire noncanonical patterns. H3K4me3 and H3K27me3 form noncanonical broad domains in oocytes, which are transiently inherited to the maternal allele of embryos (except for promoter H3K27me3). The sperm H3K4me3 and H3K27me3 quickly attenuate after fertilization. Weak and extremely large domains of H3K4me3 (at gene-rich regions) and H3K27me3 (at gene deserts) are de novo established on the paternal genome in zygotes. Concomitant with ZGA, both maternal and paternal H3K4me3 are reprogrammed to the canonical patterns, while the distal H3K27me3 domains persist until blastocyst, before being transformed into a canonical state in postimplantation embryos. Bivalency at developmental genes exists in mature gametes but is missing in preimplantation embryos. In E6.5 epiblast, H3K27me3 and unusually strong H3K4me3 form "super bivalency" (green), which is subsequently attenuated at E7.5. In mouse sperm, H2AK119ub resides at the promoters of canonical Polycomb targets. In mouse oocytes, it forms broad distal domains in H3K27me3 marked PMDs, and also occurs at active promoters associated with H3K4me3. Upon fertilization, H2AK119ub undergoes drastic changes, with global resetting of sperm signals but brief inheritance of oocyte H2AK119ub in one-cell embryos. H2AK119ub then rapidly remodels (mainly from the paternal allele but also partially from the maternal allele) and adopts similar patterns between the two alleles from the two-cell stage. After implantation, H2AK119ub and H3K27me3 become colocalized again at developmental gene promoters. H3K9me3 marks both a subset of promoters and LTRs in gametes. After fertilization, H3K9me3 is globally reset in an allele-specific manner, and the asymmetrical distribution of H3K9me3 persists to blastocyst. H3K36me3 enriches at actively expressed gene bodies in gametes. After fertilization, H3K36me3 is globally removed and is then reestablished upon ZGA. The enrichment of epigenetic modification is indicated by the widths and shades of the bars.

totipotent zygote then develops to blastocyst containing the pluripotent inner cell mass (ICM), that subsequently produces germ layers during gastrulation and, ultimately, the whole organism (Chazaud and Yamanaka 2016). During this process, epigenetic regulation plays critical roles to ensure precise spatiotemporal gene regulation (Bird 2002; Kouzarides 2007) and successful early development (Burton and Torres-Padilla 2014; Eckersley-Maslin et al. 2018; Xu and Xie 2018). Aberrant epigenetic reprogramming leads to severe developmental defects and diseases (Greenberg and Bourc'his 2019; Jambhekar et al. 2019). However, it has long been enigmatic how the epigenomes are globally reprogrammed in mammalian early development at the molecular level. Furthermore, the role of the epigenome in early development remains elusive, with mechanistic studies often hindered by the limited amount of biological material that can be obtained from embryos. Recent advances in low-input or single-cell chromatin analysis begin to illuminate specific aspects of chromatin regulation during gametogenesis and embryogenesis. Here, we summarize the dynamics of the epigenomes in gametogenesis and early development, their functions and the possible mechanisms underlying the drastic changes. Last, we highlight crucial questions that remain unanswered.

## EPIGENOME REPROGRAMMING DURING EARLY DEVELOPMENT

### DNA Methylation

5-methylcytosine (5mC) is a prevalent epigenetic mark in the mammalian genome, existing predominantly in CpG dinucleotides. It is essential for development by regulating genomic imprinting, transposon silencing, X chromosome inactivation (XCI), and gene repression (Bird 2002; Smith and Meissner 2013). In mammals, DNA methylation is established by de novo methyltransferases DNMT3A and DNMT3B, and maintained by DNMT1 through cell division, while active DNA demethylation is facilitated by the ten-eleven translocation (TET) methylcytosine dioxygenase family (Kohli and Zhang 2013; Pastor et al. 2013; Li and Zhang 2014). During germline development, PGCs first undergo extensive genome-wide DNA demethylation (Guibert et al. 2012; Seisenberger et al. 2012; Vincent et al. 2013), followed by sex-specific de novo DNA methylation (Fig. 1; Stewart et al. 2016). The proper establishment of DNA methylome is essential for spermatogenesis. In mouse, loss of DNMT3A or DNMT3L (a DNMT3A/B cofactor) causes catastrophic meiotic arrest in spermatogonia (Walsh et al. 1998; Bourc'his and Bestor 2004). Similarly, the mutation of DNMT3C, a male fetal germ cell-specific DNA methyltransferase, leads to derepression of young transposable elements and infertility (Barau et al. 2016). DNA methylation, however, appears to be dispensable for mouse oogenesis, as *Dnmt3a* or *Dnmt3l* knockout does not cause apparent oocyte developmental defects (Smallwood et al. 2011; Kobayashi et al. 2012; Shirane et al. 2013), although oocyte methylation is critical for early embryogenesis. This is perhaps not surprising since the de novo DNA methylation only occurs in late-stage oocytes (Stewart et al. 2016; Sendžikaite and Kelsey 2019; Yan et al. 2021). Notably, the mouse oocyte has a distinct DNA methylome in which only transcribed regions are highly methylated (Kobayashi et al. 2012; Shirane et al. 2013). This is attributed to the notion that Pol II can recruit SETD2 for H3K36me3 deposition, which further leads to the recruitment of DNMT3A (Dhayalan et al. 2010; Baubec et al. 2015; Dukatz et al. 2019). A major function of such transcription-dependent DNA methylation is to establish maternal imprints often by exploiting oocyte-specific promoters upstream of the imprinting control regions (ICRs) (Chotalia et al. 2009; Bartolomei and Ferguson-Smith 2011; Brind' Amour et al. 2018; Xu et al. 2019). Meanwhile, restricting DNA methylation to transcribed regions in mouse oocytes may also avoid undesired methylation of the paternal imprints. Intriguingly, while DNMT1 is dispensable for the establishment of the oocyte DNA methylome (Shirane et al. 2013), its activity needs to be strictly harnessed by STELLA, which sequestrates UHRF1 (a key cofactor of DNMT1) (Li et al. 2018b). Deletion of *Stella* results in aberrant

accumulation of DNA methylation by DNMT1 genome wide, which interferes with ZGA (Li et al. 2018b). Notably, in the mouse male germ cells, NSD1 and H3K36me2 assume similar roles as SETD2 and H3K36me3 to establish the bulk DNA methylome (Shirane et al. 2020).

After fertilization, the parental genomes undergo global DNA demethylation (except for ICRs and some retrotransposons) through both active and passive mechanisms (Fig. 1; Smith et al. 2012; Guo et al. 2014; Shen et al. 2014; Wang et al. 2014). DNA methylation at ICRs controls allele-specific expression of a small subset of genes that play important roles in placenta, postnatal development, and brain functions (for review, see Tucci et al. 2019). Notably, de novo DNA methylation, although weak, also occurs amid global demethylation, and is subjected to TET-mediated DNA demethylation (Amouroux et al. 2016). During mouse somatic cell nuclear transfer (SCNT), such de novo methylation is suggested to impede ZGA and cloning efficiency (Gao et al. 2018b). In mouse, the global DNA methylation is quickly reestablished after implantation (Smith et al. 2017; Zhang et al. 2018b). The extraembryonic tissues, such as the placenta, are relatively hypomethylated compared to embryonic lineages, presumably forming epigenetic barriers (Schroeder et al. 2015; Smith et al. 2017; Zhang et al. 2018b). Similar findings were made in cultured human embryos from day 5 to day 14 (Zhou et al. 2019). Nevertheless, despite the detailed characterization, the function of postfertilization global DNA methylation resetting remains elusive. A plausible hypothesis is that it equalizes the two distinct gametic methylomes (except for ICRs). The demethylation may also be a prerequisite for the emergence of extraembryonic tissues. Another intriguing possibility is that the postfertilization global demethylation may facilitate the elongation of telomeres in early embryos, as observed in mouse embryonic stem cells (mESCs) (Gonzalo et al. 2006; Dan et al. 2017). Future studies are warranted to test these models.

## HISTONE MODIFICATIONS

The posttranslational modifications of histones are fundamental epigenetic regulators that control many crucial cellular processes, including transcription, DNA repair, and DNA replication (Kouzarides 2007; Lawrence et al. 2016). Mounting evidence also shows that they play key roles in regulating spatial-temporal gene expression during gametogenesis and early embryo development.

### *H3K4me3*

Although most histones in mature spermatozoa are replaced with protamine, the residual histones are still extensively modified (Gold et al. 2018). For example, H3K4me3, a hallmark of permissive promoters that can recruit chromatin remodelers and transcriptional machinery (Ruthenburg et al. 2007), remains preferentially enriched at CG-rich promoters in sperm as in most other cell types (Hammoud et al. 2009, 2014; Erkek et al. 2013). In growing oocytes, H3K4me3 is similarly restricted to active promoters. However, it becomes accumulated as broad domains at both promoters and distal regions in more mature oocytes (Fig. 1; Dahl et al. 2016; Liu et al. 2016b; Zhang et al. 2016; Hanna et al. 2018b). Such noncanonical H3K4me3 (ncH3K4me3) domains found in oocytes occur almost exclusively in partially methylated DNA domains (PMDs), which are essentially nontranscribed regions (Dahl et al. 2016; Zhang et al. 2016; Hanna et al. 2018b). The fully DNA-methylated regions are protected against ncH3K4me3 by DNA methylation in conjunction with H3K36me3, as SETD2 deficiency results in the loss of H3K36me3 and DNA methylation, and ectopic invasion of H3K4me3 (Hanna et al. 2018b; Xu et al. 2019). Notably, the ncH3K4me3 domains are deposited mainly by MLL2 (KMT2B) (Hanna et al. 2018b), which is also responsible for depositing H3K4me3 at poised promoters in mESCs (Hu et al. 2013; Denissov et al. 2014) and postimplantation embryos (Xiang et al. 2020) in a transcription-independent manner. Importantly, ablation of MLL2 leads to anovulation and oocyte death (Andreu-Vieyra et al. 2010). Intriguingly, either deficiency of *Mll2* (Andreu-Vieyra et al. 2010) or overexpression of the H3K4me3 demethylase *Kdm5b* (Zhang et al. 2016) disrupts genome silencing in late-stage full-grown oocytes (FGOs). Al-

though the underlying mechanism is currently unknown, such repressive function contrasts with that of H3K4me3 at active promoters. For example, the CXXC finger protein 1 (CFP1) is a component of the histone H3K4me3 methyltransferase SETD1A/B, which functions at constitutively active promoters (Lee and Skalnik 2005; Clouaire et al. 2012). Loss of CFP1 causes global down-regulation of H3K4me3 and transcription, as well as the failure of mouse oocyte maturation (Yu et al. 2017; Sha et al. 2018). These data are in line with the notion that different H3K4me3 methyltransferase complexes have distinct targets (Hu et al. 2017; Douillet et al. 2020).

Upon fertilization, the paternal H3K4me3 quickly diminishes (Lepikhov and Walter 2004; Lepikhov et al. 2008; Zhang et al. 2016), which may be linked to the extensive protamine-histone exchange (Burton and Torres-Padilla 2014). It is subsequently reestablished in late one-cell mouse embryos, but in a noncanonical pattern, forming weak but extremely large (up to several Mbs) domains in gene-rich regions (Zhang et al. 2016). By contrast, the maternal H3K4me3 is briefly inherited to zygotes. Both maternal and paternal H3K4me3 are then reprogrammed to the canonical patterns at the two-cell stage in a ZGA-dependent manner (Fig. 1; Dahl et al. 2016; Liu et al. 2016b; Zhang et al. 2016). This is accompanied by a decrease of global H3K4me3 in immunofluorescence, executed by two lysine demethylases KDM5A/5B that are activated during ZGA (Dahl et al. 2016). Knocking down these enzymes leads to embryonic lethality (Dahl et al. 2016). Intriguingly, ncH3K4me3 is absent in human germinal vesicle (GV) oocytes (Xia et al. 2019). Instead, de novo broad domains of H3K4me3 occur in CpG-rich, accessible regions in human pre-ZGA embryos, although its function remains unknown (Xia et al. 2019). Therefore, diverse mechanisms regulate H3K4me3 in mouse and human embryos.

### *H3K27me3*

Polycomb repressive complex 2 (PRC2) is responsible for the deposition of the histone modification H3K27me3. Both PRC2 and H3K27me3 are evolutionarily conserved epigenetic regulators, which frequently repress key developmental genes and thus help maintain cell identity (Margueron and Reinberg 2011; Di Croce and Helin 2013). H3K27me3 is also enriched at developmental gene promoters in sperm (Hammoud et al. 2009, 2014; Brykczynska et al. 2010; Erkek et al. 2013). Similar to H3K4me3, widespread distal H3K27me3 domains are also found in PMDs in mouse oocytes (Figs. 1 and 2A; Liu et al. 2016b; Zheng et al. 2016). Despite its prevalence, oocyte H3K27me3 seems to be nonessential for oogenesis, since the oocyte-specific knockout of EED, a core component of PRC2 complex, does not cause notable oocyte developmental defects (Inoue et al. 2018; Prokopuk et al. 2018). However, knockout of *Ring1a*/*Ring1b* in oocytes, the key components of Polycomb repressive complex 1 (PRC1) that catalyzes H2AK119 monoubiquitination (H2AK119ub), leads to massive gene derepression, developmental defects in oocytes, and subsequent one-cell arrest after fertilization (Posfai et al. 2012; Du et al. 2020). These data are in agreement with the notion that PRC1 and its modification H2AK119ub are the major transcription repressors, while PRC2 and H3K27me3 facilitate such repression (Fursova et al. 2019; Blackledge et al. 2020; Tamburri et al. 2020). Upon fertilization, oocyte H3K27me3 at promoters of developmental genes is mostly lost, including at *Hox* gene promoters (Fig. 2A; Liu et al. 2016b; Zheng et al. 2016). The paternal H3K27me3 is quickly erased in zygotes, followed by gradual de novo formation of megabase-size broad domains of H3K27me3 in gene deserts (Zheng et al. 2016), although their functions remain unclear.

Intriguingly, the distal domains of H3K27me3 from oocytes can persist until blastocyst stage (Zheng et al. 2016). These maternally inherited H3K27me3 domains were proven to function as an imprinting mark and dictate a small set of paternal-specific genes in early mouse embryos, similar to DNA methylation-mediated imprinting (Fig. 2B; Inoue et al. 2017a; Chen and Zhang 2020). These genes include *Xist* (Inoue et al. 2017b), the master regulator of XCI (Lee 2005). In female mouse embryos, the maternal *Xist* locus is coated with a broad H3K27me3 domain inherited from oocytes, leaving the paternal copy specifically expressed, which initiates "imprinted XCI" (Fig. 2B; Inoue et al. 2017b). Abla-

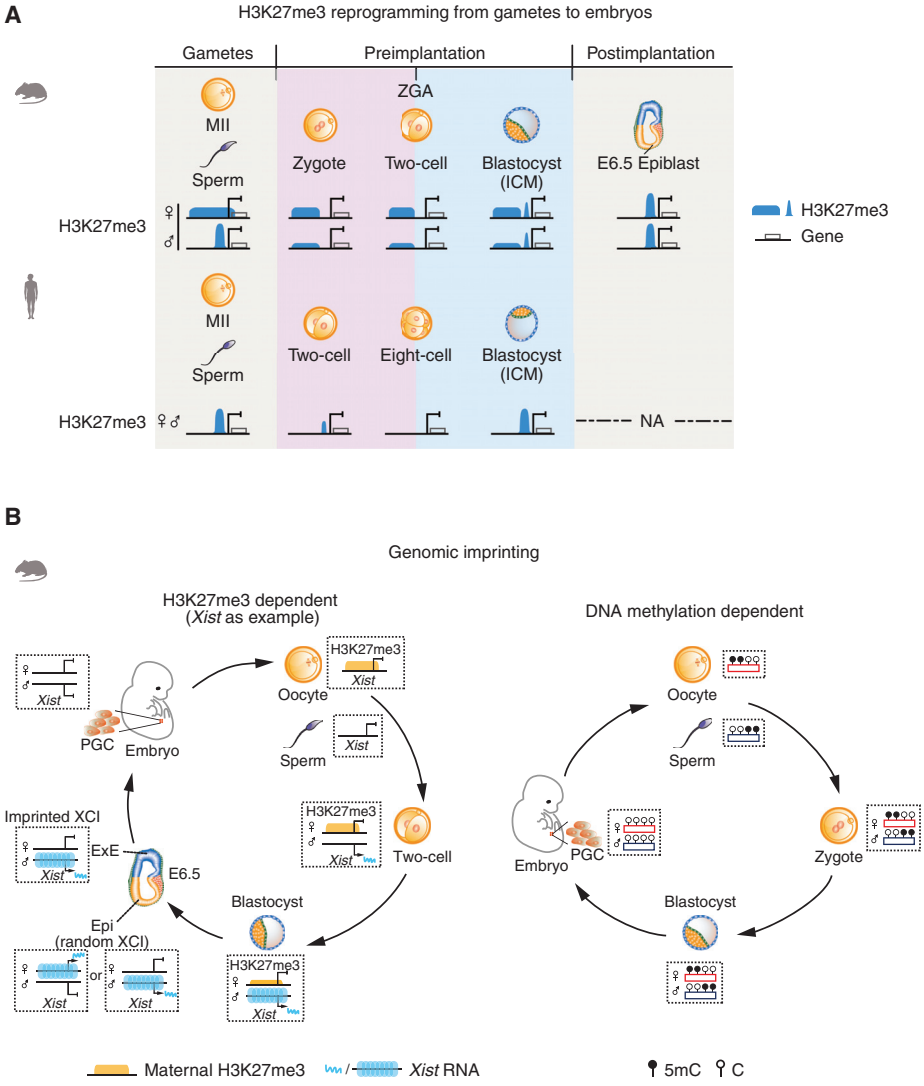


**Figure 2.** The H3K27me3 reprogramming from gametes to embryos and genomic imprinting. (*A*) The schematics show the dynamics of H3K27me3 (blue) in gametes and early embryos in mouse and human. In mouse, broad domains of H3K27me3 from oocytes are transiently inherited to embryos until blastocyst (except for promoter H3K27me3). The sperm H3K27me3 is quickly removed after fertilization. Canonical H3K27me3 is established at promoters in blastocyst and in postimplantation embryos. By contrast, in both human oocytes and sperm, H3K27me3 exhibits canonical distributions. After fertilization, H3K27me3 is globally removed before zygotic genome activation (ZGA) and is reestablished as early as the morula stage. (NA) Data not available. (B) (*Left*) A schematic model showing H3K27me3-dependent imprinting (*Xist* as an example) in mouse. Oocyte-inherited H3K27me3 domains repress maternal *Xist* in mouse female embryos, leaving the paternal copy specifically expressed and initiates the imprinted X chromosome inactivation (XCI). In postimplantation embryos, the oocyte-inherited H3K27me3 domain at the *Xist* locus is lost. Epiblast (Epi) undergoes random XCI, while the imprinted XCI persists in the extraembryonic lineages, presumably due to additional epigenetic repression mechanisms. The inactive X chromosome is reactivated in the primordial germ cells (PGCs). (*Right*) A schematic model showing DNA methylation-dependent imprinting in mouse. Oocyte and sperm establish distinct DNA methylome and differentially methylated imprinting control regions (ICRs) or imprints during the gametogenesis. Imprints can survive the global DNA demethylation during preimplantation and is well maintained thereafter, directing allelic gene expression. They are, however, erased in PGCs, paving the way for imprint establishment for the next generation. (ICM) Inner cell mass.

tion of *Eed* in oocytes leads to random X-inactivation in female embryos (Inoue et al. 2018; Harris et al. 2019). Besides *Xist*, a small subset of genes with roles in placental development, such as *Slc38a4*, *Sfmbt2*, and *Grab1*, is also imprinted by oocyte-derived H3K27me3 (Inoue et al. 2017a). Intriguingly, while the oocyte-inherited H3K27me3 is lost in postimplantation embryos (Zheng et al. 2016; Inoue et al. 2017b; Chen et al. 2019b), the imprinted states of these genes (*Platr20*, *Slc38a4*, *Gm32885*, *Gab1*, *Phf17*, and *Smoc1*) are preserved in extraembryonic tissues by maternal-specific de novo DNA methylation (Chen et al. 2019b; Hanna et al. 2019), suggesting that DNA methylation and H3K27me3 act together to safeguard their imprinting. The importance of such H3K27me3-mediated imprinting was supported by data from the SCNT embryos, where oocyte H3K27me3-mediated imprinting is apparently missing (Matoba et al. 2018). Artificially forcing the monoallelic expression of these H3K27me3-controlled imprinted genes by allele-specific gene deletion can substantially improve mouse SCNT development (Wang et al. 2020). Interestingly, such H3K27me3-mediated imprinting appears to be missing in human. In human oocytes, H3K27me3 is strongly enriched at developmental gene promoters in a canonical pattern (Xia et al. 2019). Global H3K27me3 is erased after fertilization by the eight-cell stage, when ZGA happens. Embryonic H3K27me3 is subsequently restored at developmental genes in morulae and blastocysts (Fig. 2A; Xia et al. 2019; Zhang et al. 2019b). These results are consistent with the reported absence of imprinted XCI in human (Okamoto et al. 2011; Petropoulos et al. 2016). Mechanistically, in contrast with their abundant presence in mouse, the PRC2 core components, EED and SUZ12, are not expressed in human oocytes or pre-ZGA embryos, and are only activated after ZGA (Saha et al. 2013; Xia et al. 2019). These findings highlight the divergence of epigenetic regulation in early development among different species.

### *Bivalent H3K4me3 and H3K27me3*

The "bivalent marks" refer to the co-occupancy of H3K4me3 and H3K27me3 at the promoters, often at developmental genes (Azuara et al. 2006; Bernstein et al. 2006). By bearing both permissive and repressive modifications, the bivalent marks are postulated to poise silenced key developmental genes for rapid reactivation upon cell differentiation. The bivalent marks widely exist in gametes, somatic cells, and PGCs (Vastenhouw and Schier 2012; Sachs et al. 2013; Hammoud et al. 2014). However, they are briefly absent in preimplantation embryos in mouse and human (Liu et al. 2016b; Zheng et al. 2016; Xia et al. 2019), with the underlying mechanisms and functions being unclear. One interesting possibility is that preimplantation embryos possess totipotency and pluripotency, while bivalent marks predominantly function during cell differentiation. Consistently, by E6.5, H3K27me3 and unusually strong H3K4me3 are restored at developmental gene promoters in the mouse epiblast, forming "super bivalency" (Fig. 1; Xiang et al. 2020). The "strong H3K4me3" is then quickly attenuated in fate-committed lineages and further decreases in somatic cells. Genes marked by "super-bivalency" also show strong spatial interactions as determined by Hi-C analysis (Xiang et al. 2020). In mESCs, such strong interactions rely on PRC1 and can help H3K27me3 spreading to regions away from "nucleation sites" (Schoenfelder et al. 2015; Oksuz et al. 2018; Kraft et al. 2020). Mechanistically, KMT2B (MLL2) is responsible for the "strong H3K4me3" at E6.5 but becomes partially dispensable by E8.5, as *Kmt2b* mutant embryos fail to activate a subset of developmental genes and die at E10.5 (Glaser et al. 2006; Xiang et al. 2020). As bivalent promoters are often intermediately accessible and enriched for paused Pol II (Stock et al. 2007; Brookes et al. 2012; Tee et al. 2014), it is speculated that "super-bivalency" may allow developmental genes to rapidly respond to developmental cues upon swift cell-fate decision during early lineage specification (Xiang et al. 2020). In addition, a subset of bivalent promoters is regulated by DPPA2/DPPA4 in mESCs, which safeguards promoter bivalency and prevents DNA methylation (Eckersley-Maslin et al. 2020; Gretarsson and Hackett 2020). Their roles in bivalency and differentiation in embryos are interesting topics for future studies.

### *H2AK119ub*

H2AK119ub, deposited by PRC1, preferentially colocalizes with H3K27me3 at the promoters of developmental genes in most cell types including mouse sperm (Schoenfelder et al. 2015; Chen et al. 2021; Mei et al. 2021; Zhu et al. 2021). Similar to H3K27me3, H2AK119ub in mouse oocytes also exhibits a noncanonical distribution by forming broad domains in PMDs (Chen et al. 2021; Mei et al. 2021; Zhu et al. 2021). Interestingly, it also covers a fraction of active promoters marked by H3K4me3 (Chen et al. 2021; Mei et al. 2021; Zhu et al. 2021). H2AK119ub and H3K27me3 undergo distinct reprogramming dynamics in mouse early embryos. Upon fertilization, H2AK119ub, but not H3K27me3, is retained at promoters of developmental genes, and acute depletion of H2AK119ub in one-cell embryos causes derepression of developmental genes during ZGA and four-cell arrest, suggesting that H2AK119ub protects preimplantation embryo development from precocious expression of developmental genes when H3K27me3 is absent (Chen et al. 2021). Distal maternal H3K27me3 is highly stable and persists to blastocyst, which shows distinct pattern from that of the paternal allele. By contrast, H2AK119ub is much more dynamic after fertilization and the two alleles already adopt similar distributions by the two-cell stage (Chen et al. 2021; Mei et al. 2021; Zhu et al. 2021). Finally, H2AK119ub and H3K27me3 become colocalized again by exhibiting canonical patterns after implantation (Figs. 1 and 2A; Chen et al. 2021; Mei et al. 2021).

Interestingly, H2AK119ub has a complex interplay with H3K27me3 at maternal H3K27me3-controlled imprinted genes. Acute removal of H2AK119ub in mouse one-cell embryos does not affect H3K27me3-mediated imprinting at least by the four-cell stage (Chen et al. 2021), suggesting that H2AK119ub is dispensable for the maintenance of these H3K27me3 imprints. However, oocyte-specific knockout of *Pcgf1* and *Pcgf6*, two key components of variant PRC1, leads to partial loss of H3K27me3 imprinting in both FGOs and morula (Mei et al. 2021), implying that H2AK119ub is involved in the establishment of some H3K27me3-mediated imprinting. Genes that lose H3K27me3 upon the *Pcgf1* and *Pcgf6* mutations also tend to be derepressed in FGOs (Mei et al. 2021). These findings highlight distinct roles and intricate cross talks between H2AK119ub and H3K27me3 in mouse early embryos, where H2AK119ub is more dynamic and can exert immediate repression, while H3K27me3 is relatively more stable and may serve as silencing memories.

### *H3K36me2/3*

Methylation of H3K36 plays critical roles in transcription fidelity, RNA splicing, DNA replication, and DNA repair (Wagner and Carpenter 2012; Wozniak and Strahl 2014). H3K36me3 often enriches at actively expressed gene bodies, while H3K36me2 occupies both genic and intergenic regions (Wagner and Carpenter 2012; Wozniak and Strahl 2014; Weinberg et al. 2019). Both marks can recruit DNMT3A/B and subsequently specify patterns of DNA methylation (Dhayalan et al. 2010; Baubec et al. 2015; Dukatz et al. 2019; Weinberg et al. 2019). In mouse oocytes, DNA methylation is deposited to actively transcribed regions guided by H3K36me3, and a major function for such H3K36me3-guided DNA methylation is to establish maternal imprints (Chotalia et al. 2009; Bartolomei and Ferguson-Smith 2011; Kelsey and Feil 2013; Xu et al. 2019). Meanwhile, DNA methylation and H3K36me3 may also work synergistically to protect transcribing regions from H3K4me3 and H3K27me3, as observed in *Setd2*-deficient oocytes (Hanna et al. 2018b; Xu et al. 2019). As a result, *Setd2*-deficient oocytes show developmental defects and subsequent one-cell embryo arrest after fertilization (Xu et al. 2019). Spindle exchange experiments showed that such early arrest was mainly caused by cytosolic defect, as 54% of embryos reconstructed with wild-type (WT) cytoplasm and *Setd2*-deficient chromatin can develop to blastocyst. These embryos, however, eventually died after implantation presumably due to the loss of imprints (Xu et al. 2019). By contrast, in male germline, it is NSD1 and its catalytic product H3K36me2, but not SETD2 and H3K36me3, that direct the majority of de novo DNA methylation and protect transcribing regions from the

spreading of H3K27me3 (Shirane et al. 2020). Male mice with ablated *Nsd1* are infertile with hypogonadism and cannot generate mature spermatozoa (Shirane et al. 2020). These results indicate dimorphic mechanisms in DNA methylation establishment during gametogenesis. Why oocyte and sperm employ different H3K36 methylation to guide de novo DNA methylation awaits further investigation. After fertilization, H3K36me3 from both alleles is largely lost, before it reappears concomitant with ZGA (Fig. 1; Xu et al. 2019).

### *H3K9me3*

H3K9me3 is a repressive mark that often decorates constitutive heterochromatin (Becker et al. 2016; Allshire and Madhani 2018). Disrupting H3K9me3 writers or erasers causes severe phenotypes in both oocytes and embryos. For example, mouse oocytes with deficient SETDB1, an H3K9 methyltransferase, suffer impaired meiosis and failure in silencing ERVK, ERVL, and MaLR retrotransposons (Eymery et al. 2016; Kim et al. 2016). Zygotic *Setdb1*-null embryos are lethal around implantation with defects in ICM growth (Dodge et al. 2004). Double knockout of H3K9 methyltransferase SUV39H1/2 leads to prenatal lethality in mice (Peters et al. 2001). Meanwhile, excessive H3K9me3 also needs to be curbed as the ablation of KDM4A, an H3K9me3 demethylase in oocytes, causes aberrant H3K9me3 invasion to the broad H3K4me3 domains, subsequently leading to impaired activation of genes and transposable elements during ZGA and preimplantation lethality (Sankar et al. 2020). H3K9me3 regulates mouse embryo development at least in three major aspects: facilitating the remodeling of heterochromatin, repressing repeats, and regulating lineage specification.

Mouse preimplantation embryos are featured with immature heterochromatin characterized by the absence of classic constitutive heterochromatin markers, such as HP1α and H4K20me3 (Wongtawan et al. 2011). The H3K9me3 methyltransferase SUV39H1 protein is not detected until the eight-cell stage (Burton et al. 2020). De novo H3K9me3 occurs in one-cell embryos (Wang et al. 2018; Burton et al. 2020), as ChIP-seq analyses confirmed that H3K9me3 undergoes a global resetting on both alleles after fertilization (Fig. 1; Wang et al. 2018). On the paternal genome, de novo H3K9me3 is mediated by SUV39H2, but is nonrepressive and instead bookmarks promoters for compaction at later stages (Burton et al. 2020). Such nonrepressive, immature heterochromatin appears to be essential for early development, as forced precocious expression of *Suv39h1* restores constitutive heterochromatin but impairs embryonic development especially beyond the morula stage (Burton et al. 2020). Improper reprogramming of H3K9me3 in SCNT embryos results in insufficient gene activation in somatic H3K9me3-marked regions and poor development to blastocyst (Matoba et al. 2014). Such preimplantation developmental defects can be rescued by overexpression of the H3K9me3 demethylases *Kdm4d* or *Kdm4b*, or by knockdown of H3K9 methyltransferase *Suv39h1/2* in donor cells in mouse (Matoba et al. 2014; Liu et al. 2016a). Similar findings were made in pig (Ruan et al. 2018), bovine (Liu et al. 2018a), monkey (Liu et al. 2018b), and human (Chung et al. 2015), suggesting that H3K9me3 is an evolutionarily conserved epigenetic barrier for cell-fate reprogramming.

After fertilization, a large portion of LTRs (long terminal retrotransposons) are activated (Peaston et al. 2004), possibly because of the relief of global epigenetic repression. The subsequent repression of LTRs coincides with the gradual reestablishment of H3K9me3 (Wang et al. 2018) and requires the histone chaperone chromatin assembly factor 1 (CAF-1) (Hatanaka et al. 2015; Wang et al. 2018). Knocking down the methyltransferases *Suv39h1/2* leads to increased expression of LTRs in morula but not at the two-cell stage (Hatanaka et al. 2015; Burton et al. 2020), reinforcing the notion that H3K9me3 is repressive only in late-stage embryos.

Whereas H3K9me3 is primarily present in constitutive heterochromatin and transposons, it is also observed at lineage-specific genes, where it acts as a barrier for cell-fate changes by preventing precocious activation of lineage-incompatible genes (Becker et al. 2016). For example, the distributions of promoter H3K9me3 differ significantly between intra- and extraembryonic tissues of E6.5

and E7.5 embryos (Wang et al. 2018). Uncommitted germ-layer cells transiently employ high levels of H3K9me3 to repress genes involved in lineage specification, which are subsequently removed during differentiation to allow tissue-specific gene expression (Nicetto et al. 2019). Consequently, perturbation of H3K9me3 leads to aberrant lineage-specific gene expression (Nicetto et al. 2019). For example, mouse livers with endoderm-specific *Setdb1/Suv39h1/2* triple-knockout resulted in the failed induction of hepatocyte-specific genes and aberrant expression of inappropriate lineage genes, concomitant with the loss of H3K9me3 and heterochromatin (Nicetto et al. 2019).

## TRANSPOSABLE ELEMENTS

Transposable elements (TEs) occupy almost half of the mouse and human genome (Lander et al. 2001; Mouse Genome Sequencing Consortium et al. 2002; de Koning et al. 2011). It has been increasingly evident that these elements, once thought as "junk DNA," drive genetic innovation during evolution by introducing regulatory elements (such as promoters and enhancers) and transcription factor-binding sites (Rebollo et al. 2012; Chuong et al. 2017; Jangam et al. 2017; Bourque et al. 2018). MERVL, a member of endogenous retroviruses (ERVs), is actively transcribed during minor ZGA in mouse embryos (Svoboda et al. 2004), and was shown to regulate mouse preimplantation development (Huang et al. 2017). MERVL is reported to initiate hundreds of two-cell-specific transcripts in two-cell-like cells (2CLC), a rare and transient cell population in mESCs (Macfarlan et al. 2012; Genet and Torres-Padilla 2020). Notably, overexpressing DUX, a transcription factor specifically expressed during minor ZGA, can activate MERVL transcription and induce 2CLCs in mESCs through the DUX-miR-344-ZMYM2 pathway (De Iaco et al. 2017; Hendrickson et al. 2017; Whiddon et al. 2017; Yang et al. 2020). DUX itself is activated by two upstream transcription factors DPPA2/DPPA4 (Eckersley-Maslin et al. 2019) and negative elongation factor A (NELFA) (Hu et al. 2020). Apart from DUX, ZSCAN4, a nonconventional transcription factor (Falco et al. 2007; Ko 2016; Srinivasan et al. 2020), can also activate MERVL (Zhang et al. 2019a), in addition to its role in telomere elongation and genome integrity in mESCs (Ko 2016). However, ZSCAN4, in contrast to DUX, fails to do so in the absence of DPPA2/DPPA4 in mESCs. It was proposed that ZSCAN4 is not the driving factor but instead is a stabilizer to initiate the ZGA (De Iaco et al. 2019; Eckersley-Maslin et al. 2019). Notably, the *Dux*-knockout embryos show only minor defects of ZGA and MERVL transcription, and the majority of them can develop to term (Chen and Zhang 2019; Guo et al. 2019; De Iaco et al. 2020). DPPA2/DPPA4 double-null mice undergo normal embryogenesis but die perinatally (Nakamura et al. 2011). Therefore, these data suggest that additional ZGA regulators exist in embryos.

Long interspersed element-1 (LINE1), a subclass of non-LTR transposons, also plays a vital role in mouse embryo development (Beraldi et al. 2006; Jachowicz et al. 2017; Percharde et al. 2018). These elements are abundantly transcribed in mouse oocytes and fertilized embryos, before undergoing repression after the two-cell stage (Fadloun et al. 2013; Jachowicz et al. 2017). LINE1 knockdown in mouse zygotes was shown to impair ZGA and lead to two-cell stage arrest (Percharde et al. 2018). Interestingly, LINE1 transcription, but not its RNA, contributes to the embryo development by decondensing chromatin (Jachowicz et al. 2017). Precocious silencing or prolonged activation of LINE1 hinders chromatin relaxation or compaction, respectively, both resulting in embryo developmental defects (Beraldi et al. 2006; Jachowicz et al. 2017). Intriguingly, LINE1 RNA could also repress *Dux* expression in mESCs along with nucleolin and KAP1/TRIM28 (Percharde et al. 2018). It remains to be determined whether this is also the case in early embryos where *Dux* also needs to be shut down in a timely manner (Guo et al. 2019). Therefore, transposon elements are integral to the transcriptional circuitry in early development. Their exact roles in ZGA, totipotency, pluripotency, and lineage commitment await further investigation.

## CHROMATIN ACCESSIBILITY

Accessible chromatin usually marks *cis*-regulatory elements, such as promoters, enhancers, insu-

lators, where *trans*-acting factors interact with DNA and regulate gene expression (Klemm et al. 2019). Genome-wide accessible chromatin landscapes in mouse gametes and preimplantation were profiled with DNase I sequencing (liDNase-seq) (Lu et al. 2016; Inoue et al. 2017a) or transposase accessible chromatin-sequencing (ATAC-seq) (Wu et al. 2016; Jung et al. 2017, 2019). Interestingly, while both ATAC-seq and DNase-seq can reproduce chromatin accessibility at later-stage early embryos, their performance in detecting open chromatin in earlier-stage embryos (such as zygotes), oocytes, and sperm varies. This likely reflects the unique chromatin states of these cells and the sensitivity of different technologies, including possible overdigestion of highly permissive chromatin. Nevertheless, a consensus picture from these data revealed that accessible chromatin in gametes and early embryos also enrich for regulatory elements such as promoters and enhancers, including at stages when transcription is silenced (Lu et al. 2016; Wu et al. 2016, 2018; Jung et al. 2017, 2019; Gao et al. 2018a; Li et al. 2018a). Interestingly, a significant fraction of open chromatin appears to be specific for pre-ZGA embryos, and is lost upon genome activation (Wu et al. 2016, 2018). Such a change may in part reflect the transition from maternal transcription factors to zygotic transcription regulators. In fact, these accessible chromatin maps have also revealed a rich repertoire of candidate transcription regulators in gametogenesis and early development (Lu et al. 2016; Wu et al. 2016, 2018; Jung et al. 2017; Gao et al. 2018a; Li et al. 2018a; Jung et al. 2019).

## 3D GENOME

In eukaryotes, the genome is packaged into a multilayer, higher-order chromatin configuration (Bickmore 2013; Gibcus and Dekker 2013; Gorkin et al. 2014; Bonev and Cavalli 2016; Misteli 2020). The chromosomes are nonrandomly distributed in interphase nucleus, occupying different chromosome territories. At the megabase scale, the genome is spatially partitioned into transcriptionally active compartment A, which preferentially resides near the nuclear speckles, and repressive compartment B, which is often associated with nuclear lamina or nucleolus (Lieberman-Aiden et al. 2009; van Steensel and Belmont 2017; Chen et al. 2018; Quinodoz et al. 2018). Topologically associating domains (TADs) exist as self-interacting domains usually with lengths of several hundred kilobase in mammals (Gibcus and Dekker 2013; Gorkin et al. 2014; Rowley and Corces 2018). They often arise via ATP-dependent loop extrusion, as cohesin extrudes chromatin until it is stopped by CCCTC-binding factor (CTCF) or other *cis*-acting factors (Sanborn et al. 2015; Fudenberg et al. 2016; Rao et al. 2017; Schwarzer et al. 2017; Vian et al. 2018; Davidson et al. 2019; Kim et al. 2019). At an even finer scale, the interactions among regulatory elements such as promoters and enhancers are crucial in regulating appropriate gene expression (Gorkin et al. 2014; Pombo and Dillon 2015; Schoenfelder and Fraser 2019). With the development of low-input or single-cell technologies to analyze chromatin organization, the dynamics of chromatin structure during gametogenesis and early embryo development begin to be unveiled, as summarized below.

### *Genome Organization in Spermatogenesis*

To transport the haploid paternal genome to the offspring, the male germ cells undergo an orchestrated developmental process from spermatogonia to mature spermatozoa, which could be briefly divided into three major phases: mitosis (the proliferation and differentiation of spermatogonia), meiosis (the formation of haploid cells), and postmeiosis spermiogenesis (when the genome is subjected to compaction accompanied with histone-protamine exchange) (Handel and Schimenti 2010). In the meiosis I prophase, the homologous chromosomes undergo pairing (during the leptotene and zygotene stage), synapse (at the pachytene stage) and desynapse (at the onset of the diplotene stage) (Zickler and Kleckner 2015). Interestingly, TADs and compartments A/B dissolve in both monkey and mouse pachytene spermatocytes, when the homologous chromosomes parallelly align along the synaptonemal complex with chromatin loops extruding from the central axis (Alavattam et al. 2019; Patel et al. 2019; Vara et al. 2019; Wang et al.

2019b; Luo et al. 2020). At the same time, transcription-correlated local compartments (refined compartments A/B) (or point interactions/transcription hubs) emerge. These data raise a possibility that the chromatin loops facilitated by synaptonemal complex (Zickler and Kleckner 2015) may be incompatible with compartments A/B and chromatin loops mediated by CTCF (Nuebler et al. 2018). In line with this idea, refined compartments A/B are attenuated in synaptonemal complex mutants (*Sycp2*), with conventional TADs and compartmentalization partially restored (Wang et al. 2019b). Furthermore, conventional compartments and TADs also reappear in mature spermatozoa (Fig. 3; Battulin et al. 2015; Du et al. 2017; Jung et al. 2017; Ke et al. 2017; Alavattam et al. 2019; Wang et al. 2019b; Luo et al. 2020), although this was not detected in a separate study using a different sperm collection method (Vara et al. 2019). Interestingly, human mature spermatozoa have no TADs, which is attributed to CTCF silencing (Fig. 3; Chen et al. 2019a). Zebrafish spermatozoa also do not have conventional TADs, but possess unique "hinge-like" chromatin domains arranged similarly as mitotic chromosomes (Wike et al. 2021). These data show that extensive chromosome reorganization occurs during spermatogenesis and distinct mechanisms underline chromatin condensation in mature sperm in different species.

### Genome Organization in Oogenesis

Oocytes are arrested at the diplotene stage for an extended time when the meiotic recombination is completed and the synaptonemal complex is largely dissembled (Handel and Schimenti 2010). Upon hormone stimulation, some oocytes undergo follicle growth, which start to accumulate proteins and RNAs for embryonic development, ultimately becoming FGOs (Bachvarova 1985; Li et al. 2010; Veselovska et al. 2015). TADs and chromatin loops can be detected in FGOs and, similar to those in soma, depend on SCC1, a key component of cohesin (Flyamer et al. 2017; Du et al. 2020; Silva et al. 2020). A meiotic-specific cohesin component, REC8, is required for the bivalent chromosome cohesion (Tachibana-Konwalski et al. 2010; Silva et al. 2020). Moreover, H3K27me3-marked compartmental domains (termed Polycomb-associating domains [PADs]) with strong interdomain interactions emerge in FGOs, concomitant with the loss of conventional compartments A/B (Flyamer et al. 2017; Du et al. 2020) and lamina-associated domains (LADs) (Fig. 3; van Steensel and Belmont 2017; Borsos et al. 2019). PADs require the PRC1 core components RING1A and RING1B, which catalyze H2AK119ub, but not the PRC2 protein EED and cohesin. *Ring1a*/*Ring1b* double knockout also partially derepresses the genes located in PADs in mouse oocytes, raising the possibility that PADs may play a role in gene silencing (Du et al. 2020). These data are in line with the notion that PRC1 is essential for both gene repression and Polycomb target interactions (Schuettengruber et al. 2017; Fursova et al. 2019; Blackledge et al. 2020; Boyle et al. 2020; Tamburri et al. 2020). Upon releasing oocytes from the diplotene arrest, PADs quickly disassemble (Du et al. 2020). When these cells are subsequently rearrested at metaphase II, the genome structure adopts a mitotic-like chromatin structure that lacks TADs, PADs, and compartments (Fig. 3; Du et al. 2017; Ke et al. 2017; Oomen and Dekker 2017). The mechanisms that lead to the formation of PADs in FGOs is currently unknown. It also remains unclear whether the collapse of chromatin around nucleolus in late-stage oocytes (Zuccotti et al. 1995) may contribute to the detachment of genome from the lamina and the emergence of PADs.

### Conserved Relaxed Chromatin Organization after Fertilization

After fertilization, a prominent feature of chromatin of mouse zygotes is that it is extremely dispersed and lacks apparent condensed organization, as revealed by electron spectroscopic imaging (Ahmed et al. 2010). Consistently, low-input or single-cell Hi-C analyses show that chromatin adopts a highly dispersed or relaxed state in the zygotes and two-cell embryos, with loops, TADs, and compartments all substantially weakened compared with those in later-stage embryos (Fig. 3; Du et al. 2017; Flyamer et al. 2017; Gassler et al. 2017; Ke et al. 2017; Collombet et al.

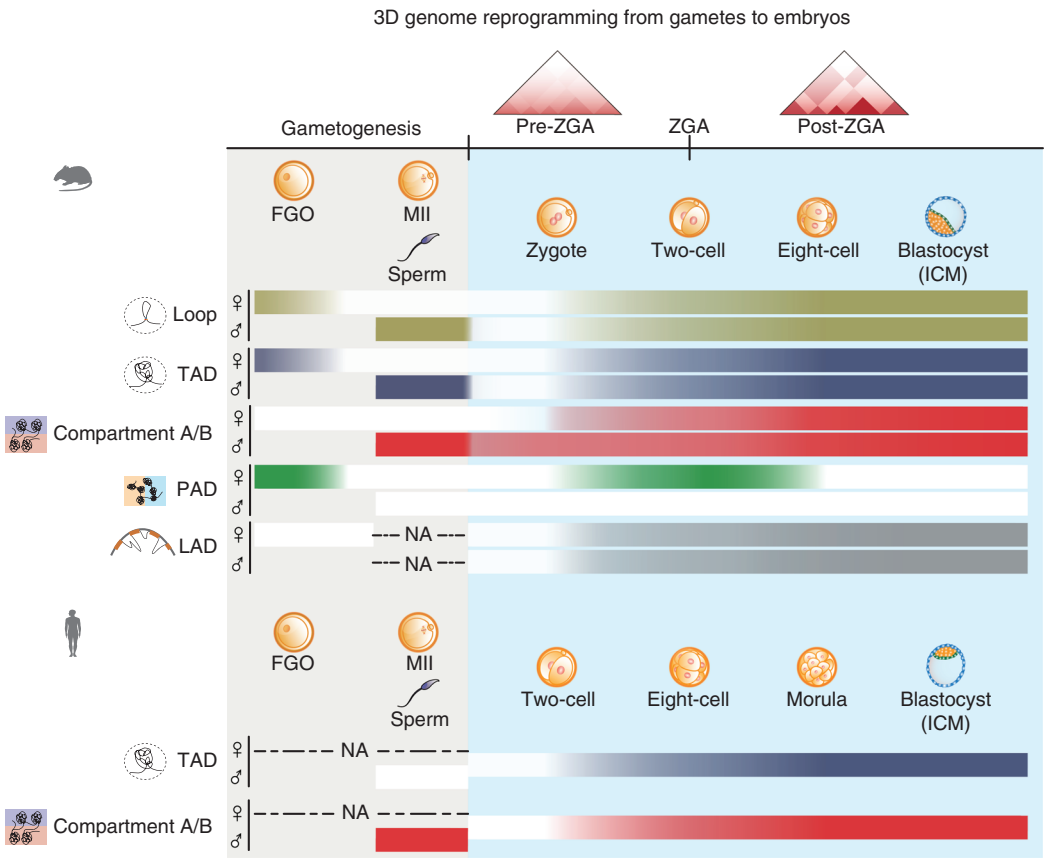


**Figure 3.** 3D genome dynamics in gametes and early embryos. The schematics showing the dynamics of higher-order chromatin structure from gametes to embryos in mouse and human. In mice, full-grown oocytes (FGOs) exhibit cohesin-independent, H3K27me3-marked compartmental domains (Polycomb-associating domains [PADs]). By contrast, topologically associating domains (TADs) become weak and compartments A/B are undetectable in FGOs. Lamina-associated domains (LADs) are also undetected in FGOs. In MII oocytes, chromatin adopts a mitotic-like chromatin structure, where compartments A/B, PADs, TADs, and loops are all lost. By contrast, mouse mature sperm shows canonical A/B compartmentalization, TADs, and loops. After fertilization, chromatin structure is dramatically dispersed, which shows weakened compartments, TADs, and loops. The genome structure is then gradually reestablished during preimplantation development. PADs briefly reappear specifically on the maternal allele from one-cell to eight-cell stages. LADs (gray) are de novo established after fertilization. Human embryos also exhibit diminished higher-order structure after fertilization, followed by consolidation of TADs and compartments A/B after zygotic genome activation (ZGA). Notably, human sperm has no typical TADs possibly due to the lack of CTCF protein. The strength of TADs, compartmentalization (compartments A/B and PADs/iPADs), and LADs are indicated by the shades of the bars. (NA) Data not available, (ICM) inner cell mass.

2020). Remarkably, the extensively relaxed chromatin organization after fertilization is evolutionarily conserved, as similar findings were also made in fly (Hug et al. 2017; Ogiyama et al. 2018), fish (Kaaij et al. 2018; Nakamura et al. 2021; Wike et al. 2021), pig (Li et al. 2020), and human (Chen et al. 2019a). How chromatin relaxation occurs and whether it regulates early development remain a mystery. Such chromatin relaxation is also found in two-cell mouse SCNT embryos, implying that the ooplasm has a potent ability to relax chromatin organization (Chen

et al. 2020; Zhang et al. 2020). Intriguingly, mimicking chromatin relaxation by pre-depletion of cohesin in the donor cells promotes the SCNT development, and this is in part via facilitating minor ZGA (Zhang et al. 2020). Further investigations are warranted to fully unravel the function of the highly dispersed chromatin state in early embryos.

### *Progressive Maturation of Chromatin Structure in Preimplantation Embryos*

Chromatin structure reestablishment appears to be an unusually slow and prolonged process during early embryogenesis. The consolidation of TADs and the segregation of chromatin compartments are not completed until the eight-cell stage in mouse (Du et al. 2017; Ke et al. 2017), and around the morula stage in human (Fig. 3; Chen et al. 2019a). The maturation of TADs appears to require ZGA in human, presumably because CTCF is lowly expressed prior to ZGA but is highly induced during ZGA (Chen et al. 2019a). This is, however, not the case in mouse and fly embryos, where ZGA is dispensable for TAD and compartment A/B maturation (Du et al. 2017; Hug et al. 2017; Ke et al. 2017), indicating that additional mechanisms exist to help relax chromatin architecture in early development. The maturation of chromatin organization also includes equalizing chromatin organization between the two alleles. In mouse zygotes, the chromatin compartment is clearly visible for the paternal genome, while the maternal genome is poorly segregated (Du et al. 2017; Flyamer et al. 2017; Ke et al. 2017). The mechanisms underlying such differences remain unknown, although it is clear that the maternal and paternal genomes are independently segregated (Duffié and Bourc'his 2013) using two bipolar spindles in zygotes (Reichmann et al. 2018), as also captured by Hi-C (Du et al. 2017). The differential compartment reprogramming lasts until the eight-cell stage (Fig. 3; Du et al. 2017; Ke et al. 2017).

Besides TADs and compartments, LADs also undergo drastic reprogramming during mouse early embryogenesis (Borsos et al. 2019). They emerge as early as in the mouse zygote, similar to compartments, where the maternal genome exhibits poorly defined LADs, which then gradually are reinforced at the two-cell stage (Fig. 3; Du et al. 2017; Ke et al. 2017; Borsos et al. 2019). Furthermore, LADs in the two-cell embryos are in a noncanonical state, as many LADs colocalize with compartment A instead of compartment B, and LADs/inter-LADs show smaller differences of AT contents (Borsos et al. 2019). These observations likely reflect the transitionary nature of chromatin organization at this stage. Intriguingly, the ectopic expression of *Kdm5b*, the H3K4me3 demethylase, erases the paternal LADs in one-cell embryos (Borsos et al. 2019). How H3K4me3 regulates paternal LADs remains unknown. Notably, PADs briefly reappear on the maternal allele from one-cell to eight-cell stages (Fig. 3), concomitant with the brief inheritance of oocyte H3K27me3 domains (Zheng et al. 2016; Collombet et al. 2020; Du et al. 2020; Chen et al. 2021; Mei et al. 2021). Unlike what happens in oocytes, PADs in early embryos depend on PRC2 (Du et al. 2020). These observations indicate that histone modifications may also contribute to the reprogramming of chromatin architecture in embryos, and chromatin architecture matures at multidimensions in early development.

## OUTSTANDING QUESTIONS

The recent exciting progress in understanding epigenetic reprogramming during early mammalian development inevitably raises many fundamental questions, as we discuss below.

1. Why do mammalian oocytes adopt noncanonical epigenomes?

Mouse oocytes adopt noncanonical epigenomes including DNA hypomethylated nontranscribing regions, broad domains of key histone modifications, and unique 3D genome structures. Why do mammalian oocytes, in contrast to sperm and soma, display so many unique features (Fig. 4)? This is particularly intriguing given zebrafish oocytes show relatively conventional epigenomes (Jiang et al. 2013; Potok et al. 2013; Zhang et al. 2018a; Zhu et al. 2019). One possibility lies in the fact that mammals require imprinting. To establish imprints, mammali-

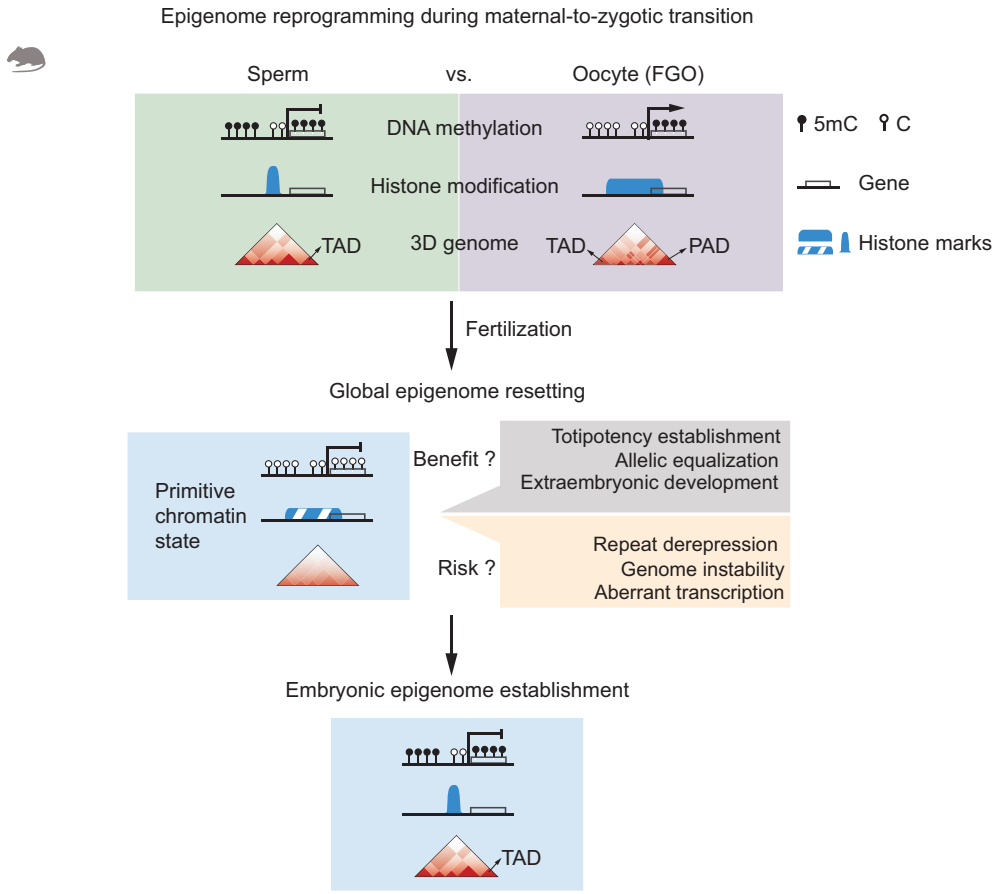


**Figure 4.** Epigenome reprogramming during maternal-to-zygotic transition (MZT). Mouse oocytes, but not sperm, adopt noncanonical epigenomes including DNA hypomethylated nontranscribing regions, broad domains of key histone modifications, and unique 3D genome structures. After fertilization, the embryos undergo global epigenome resetting, featured by the global loss of repressive epigenetic marks (such as DNA methylation), widespread presence of active histone marks, and global chromatin relaxation. The global resetting might be beneficial for the establishment of totipotency, allelic epigenome equalization, and extraembryonic tissue development. Meanwhile, it may also expose embryos for risks of repeat derepression, genome instability, and aberrant transcription. After zygotic genome activation (ZGA), the embryos stepwise establish embryonic epigenomes to restore DNA methylation, histone marks, and higher-order chromatin structure. (FGO) Full-grown oocyte, (TAD) topologically associating domain, (PAD) Polycomb-associating domain.

an oocytes exploit a transcription-dependent mechanism to establish a partially methylated genome, which contrasts the hypermethylated sperm genome (Stewart et al. 2016; Sendžikaite and Kelsey 2019). It is, however, unclear why oocytes use such a dramatically distinct DNA methylome despite the fact that only a tiny portion are true imprints. It warrants further investigation if the remaining differential methylomes are simply "passenger marks" brought by the transcription-dependent de novo DNA methylation. Alternatively, they may provide a pool of candidate imprints during evolution, especially considering the existence of species-specific imprints (Bartolomei and Ferguson-Smith 2011).

Likewise, the broad domains of histone marks in mouse oocytes, which contrast with those in sperm, set the stage for noncanonical H3K27me3 imprinting (Inoue et al. 2017a,b),

although such imprinting seems to be limited to rodents (Xia et al. 2019). Several other factors may also contribute to such noncanonical patterning of histone marks. First, the prolonged prophase-I arrest of oocytes, which lacks DNA replication and cell division, provides ample time for the deposition of histone marks and the incorporation of histone variants (the deposition of which is DNA replication-independent). For example, H3.3 plays a critical role in oocytes as the deletion of H3.3 impairs oocyte competence, concomitant with aberrant chromatin accessibility, histone modifications, and ectopic gene activation (Lin et al. 2014; Nashun et al. 2015; Smith et al. 2020). Second, the lack of DNA methylation in nontranscribing regions may allow opportunistic deposition of opposing histone marks, as evidenced in the *Dnmt3a*/*3b*-double-knockout or *Setd2*-null oocytes (Hanna et al. 2018b; Xu et al. 2019). Nevertheless, how human oocytes manage to avoid these broad domains of histone marks (such as H3K4me3) (Xia et al. 2019) remains unclear. Last, the noncanonical histone marks may be related to oocyte-specific functions. For example, noncanonical H3K4me3 appears to be required for the transcription silencing of oocytes (Zhang et al. 2016; Hanna et al. 2018b).

2. Why do early mammalian embryos require genome-wide resetting rather than region-specific refining?

Embryos undergo extensive genome-wide epigenome reprogramming upon fertilization, which is rarely observed for other biological processes. A natural hypothesis is that the global resetting can efficiently convert the epigenomes from gametes to embryos. Nevertheless, neither the global chromatin relaxation nor genome-wide erasure of repressive epigenetic marks was reported in iPSC reprogramming, an equally dramatic cell-fate conversion event (Papp and Plath 2013). First, one possibility is that the remarkable difference between fertilization and iPSC conversion may reflect the distinct developmental potency for fertilized embryos ("totipotency") and iPS cells ("pluripotency"). Perhaps the emergence of totipotency requires a globally permissive, naive chromatin state. Second, the global demethylation in early embryos may contribute to the establishment of hypomethylated extraembryonic tissues (Schroeder et al. 2015; Smith et al. 2017; Zhang et al. 2018b). Last, a third possible purpose of the dramatic reprogramming in early embryos may be to equalize the distinct epigenomes of two alleles inherited from sperm and oocytes, which arise during the establishment of imprints. As supporting evidence, zebrafish, which lack imprinting, do not undergo global DNA demethylation (Macleod et al. 1999; Jiang et al. 2013; Potok et al. 2013), but instead present locus-specific DNA methylation remodeling.

Notably, zebrafish gametes show canonical patterns of histone modifications, which are, however, rapidly lost during early embryogenesis, before being restored at regulatory elements around ZGA (Vastenhouw et al. 2010; Zhang et al. 2014, 2018a; Murphy et al. 2018; Zhu et al. 2019). The differences between DNA methylation and histone modification reprogramming in zebrafish may be related to the fact that histone marks lack an efficient maintenance mechanism, compared with DNA methylation, as their post-DNA replication recovery is usually much slower than DNA methylation (Budhavarapu et al. 2013; Almouzni and Cedar 2016). Therefore, histone marks are perhaps more difficult to be maintained during the extremely rapid embryo cleavage in early development, until the cell cycle slows down around ZGA (Kane and Kimmel 1993).

3. How do embryos achieve successful MZT?

MZT is a key process in early embryos, which transfers the developmental control from maternally inherited gene products to zygotically synthesized factors (Schultz 2002; Walser and Lipshitz 2011). Mounting data begin to reveal the existence of a "primitive" chromatin state prior to ZGA featured with widespread active marks, immature heterochromatin, and relaxed chromatin structure (Fig. 4; Xia and Xie 2020). The mechanisms underlying the noncanonical setting of the epigenome, and their roles in MZT are fascinating questions and are discussed below.

First, fertilized mouse embryos are featured by compromised heterochromatin, as manifested by the lack of chromocenters and the rapid decrease or resetting of heterochromatin epigenetic marks such as H3K9me3, H3K64me3, H4K20me3, H3K27me3, and DNA methylation (Probst et al. 2007; Aguirre-Lavin et al. 2012; Burton and Torres-Padilla 2014). The loss of heterochromatin may be important for lengthening telomeres (Ko 2016) and for eliminating cell reprogramming barriers to release zygotic genome from a constrained environment to become a totipotent state (Zhou and Dean 2015; Becker et al. 2016). Nevertheless, it presumably also creates challenges and stresses to the embryos. For example, the global loss of DNA demethylation and repressive H3K9me3 can lead to derepression of repeats that threaten genome stability (Gerdes et al. 2016; Rodriguez-Terrones and Torres-Padilla 2018) and trigger immune responses (Grow et al. 2015). However, these repeats are also exploited by embryos for transcription regulation through creating new or alternative promoters, providing or disrupting TF-binding sites, regulating chromatin accessibility, and silencing nearby genes (Gerdes et al. 2016; Rodriguez-Terrones and Torres-Padilla 2018). Meanwhile, it is perhaps not surprising that embryos employ alternative mechanisms to withstand the detrimental effects from the loss of heterochromatin. For instance, in one-cell mouse embryos, the maternally provided PRC1 and corresponding H2AK119ub temporarily assume the function of H3K9me3 in the paternal genome at pericentromeric heterochromatin to inhibit pericentric satellite expression (Puschendorf et al. 2008; Tardat et al. 2015). Similarly, while H3K27me3 is erased from its canonical targets (developmental genes) in mouse preimplantation embryos (Zheng et al. 2016), H2AK119ub maintains these developmental genes nevertheless silenced (Chen et al. 2021).

Second, despite the largely silenced transcriptional state, pre-ZGA embryos show hyperpermissive chromatin featuring widespread transcription-independent active marks and open chromatin. For example, the paternal genomes of mouse one-cell embryos transiently acquire H3K4me3 domains in gene-rich regions (Zhang et al. 2016). Likewise, human pre-ZGA embryos exhibit broad domains of H3K4me3 at CG-rich promoters and distal regions (Xia et al. 2019). In zebrafish, widespread de novo H3K27ac occupies promoters throughout the genome prior to ZGA (Zhang et al. 2018a; Sato et al. 2019). The transcription-independent active histone marks likely reflect a "primitive" state of the genome and perhaps also prepares chromatin for coming ZGA. In support of this hypothesis, histone acetylation precedes and is required for transcription elongation in zebrafish early embryos (Zhang et al. 2018a; Chan et al. 2019; Sato et al. 2019). Such hyperpermissive chromatin is likely contributed by the loss of heterochromatic marks. In addition, one-cell embryos either inherit or acquire high levels of histone variants, including H3.3, H2A.X, and TH2A (Burton and Torres-Padilla 2014; Shinagawa et al. 2014; Funaya and Aoki 2017). For example, the paternal genome incorporates H3.3-packaged nucleosomes through protamine-histone exchange in one-cell mouse embryos (van der Heijden et al. 2005; Torres-Padilla et al. 2006; Santenard et al. 2010). Consequently, embryos deficient for maternal *Hira*, which is responsible for H3.3, suffer impaired male pronucleus formation, DNA replication, and rRNA transcription (Loppin et al. 2005; Inoue and Zhang 2014; Lin et al. 2014). The abundant histone variants may also contribute to the high mobility and dispersed state of zygotic chromatin (Ooga et al. 2016). Such hyperpermissive chromatin, however, needs to be curbed upon ZGA to ensure the fidelity of transcription programs. For example, exogenous promoters can fire without enhancers in the one-cell, but not two-cell, mouse embryos, indicating a progressively repressive chromatin environment (Wiekowski et al. 1991; Majumder et al. 1993). Repression of LINE-1 may also contribute to chromatin compaction beyond the two-cell stage (Jachowicz et al. 2017). In addition, transcription activity, in particular during minor ZGA, may play a critical role in this process, as transcription inhibition prevents ZGA-associated transition of open chromatin and active histone marks (Wu et al. 2016, 2018; Zhang et al. 2016; Li et al. 2018a).

Last, early embryos employ a highly conserved relaxed 3D chromatin organization fea-

tured by the loss of TADs, loops, and compartments (Zheng and Xie 2019). It remains unclear whether the long-range enhancer–promoter interactions are also lost and reset after fertilization. If so, one intriguing question is how embryos execute transcription programs without long-distance enhancer–promoter interactions and the facilitating TADs and loops when ZGA starts. It is possible that embryos may primarily use genes or enhancers that do not require long-distance interactions, which could help prevent premature firing of developmental genes and cell-fate commitment programs. Currently, the enhancer–promoter regulatory network at the beginning of life still remains largely unknown and awaits further investigations.

4. How do early embryos establish an embryonic epigenome?

The establishment of embryonic epigenome could be divided into two waves. Embryonic active epigenetic marks are often established around ZGA in mouse and human, with H3K4me3 occupying active promoters (Dahl et al. 2016; Zhang et al. 2016; Xia et al. 2019), and H3K27ac and open chromatin appearing at both active promoters and putative enhancers (Liu et al. 2016b; Lu et al. 2016; Wu et al. 2016, 2018; Gao et al. 2018a; Li et al. 2018a; Xia et al. 2019). ZGA is required for this process, as transcription inhibition blocks the redistribution of these active marks (Dahl et al. 2016; Wu et al. 2016, 2018; Zhang et al. 2016; Xia et al. 2019). These data paint a picture in which transcription facilitates chromatin state transitions, which presumably in turn potentiate transcription, forming a positive-feedback loop. By contrast, the establishment of repressive epigenetic marks (such as H3K27me3, H3K9me3, and DNA methylation) occurs later, often around implantation (Liu et al. 2016b; Zheng et al. 2016; Smith et al. 2017; Wang et al. 2018; Zhang et al. 2018b; Nicetto et al. 2019). Why does the reestablishment of repressive marks occur at a slower pace compared to active marks? One possibility is that the absence of these repressive marks at earlier stages may be a prerequisite to ensure the embryos to retain totipotency. Consistently, the removal of H3K9me3 by the depletion of H3K9 methyltransferase SETDB1 and its binding partner KAP1 promotes the transition from mESC to two-cell-like cells, during which cells partially regain totipotent potentials (Wu et al. 2020). These two waves of embryonic epigenome establishment may ensure the coordination of step-wise developmental events that include ZGA, totipotency emergence, and cell-fate determination (Fig. 4). At the gene level, diverse signaling pathways and transcription factors are often engaged in regulating the accurate embryonic epigenome establishment. For example, WNT and FGF signaling pathways are reported to modulate the global hypomethylation and CGI methylation in the extraembryonic lineages (Smith et al. 2017). Distinct transcription factors are expected to function in the lineage-specific distribution of DNA methylation and histone marks at regulatory elements based on the motif-enrichment analysis (Smith et al. 2017; Wang et al. 2018; Zhang et al. 2018b; Xiang et al. 2020). Future studies on the establishment of embryonic epigenome will undoubtedly broaden our understanding of the arise of totipotency, pluripotency, and lineage specification during embryo development.

## CONCLUDING REMARKS

Tremendous advances in ultrasensitive chromatin analysis technologies have shown the epigenome reprogramming modes in mammalian gametogenesis and early development, and the mechanisms underlying these fascinating processes. Despite these breakthroughs, more questions arise as expected. First, with the emerging detailed maps of the epigenome, how and why these reprogramming events occur remain elusive. For example, what are the molecular mechanisms and the potential functions of the relaxed chromatin structure after fertilization? What are the key factors or events that trigger ZGA in mammals? Addressing these questions would bring the second major challenge in the field, which is the urgent need to develop innovative tools. For instance, CRISPR-based screening is a powerful tool to identify the key transcription regulators in cell lines (Alda-Catalinas et al. 2020). Yet, genome-wide screening is still a

daunting task for early embryos. This is further complicated by the presence of abundant maternal proteins that can be highly stable in oocytes and early embryos. Easy-to-use protein degradation methods, such as PROTAC (Burslem and Crews 2020), ARMeD (Ibrahim et al. 2020), or Trim-away (Clift et al. 2017), are needed for the loss-of-function studies to investigate factors of interests. The emerging new in vitro models, such as blastoid and gastruloid (for review, see Baillie-Benson et al. 2020), could simulate embryonic development and be potentially used to screen and identify key regulators in embryonic development. Ultrasensitive and single-cell technologies, preferentially with the ability to probe multi-omics, should be instrumental in deciphering the spatiotemporal chromatin dynamics in early embryos. For example, TFs play essential roles in governing transcription circuitry especially during lineage specification. Although improved ChIP and ChIC-based methods (uliChIP, itChIP, CUT&RUN, CUT&Tag, ChIL-seq, CoBATCH, ACT-seq, etc.) (Brind'Amour et al. 2015; Skene and Henikoff 2017; Ai et al. 2019; Carter et al. 2019; Harada et al. 2019; Kaya-Okur et al. 2019; Wang et al. 2019a) have been invented, these methods rely on highly sensitive antibodies that are not always accessible. As another example, enhancer–promoter interactions are still difficult to study in early development because of the sparse Hi-C data from limited research materials. Improved chromatin conformation capture methods to enrich the regulatory chromatin interactions at high resolution is urgently needed. The Oligopaint-based DNA FISH (fluorescence in situ hybridization) and CRISPR-based live-cell imaging methods that can tag numerous genomic loci simultaneously (Kempfer and Pombo 2020) may facilitate decoding how dynamic chromatin conformation contributes to gene expression during embryogenesis. Single-cell, multi-omics methods would be essential to delineate the heterogeneity of cells during early development. Thirdly, epigenome reprogramming studies across species have revealed remarkable differences between mice and human, and even between monkey and human (Hanna et al. 2018a; Chen et al. 2019a; Wang et al. 2019b; Xia et al. 2019). Applying the research framework to other species will shed light on the evolution of epigenetic reprogramming and facilitate studies for key events that are found in human but not in mouse.

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