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# Epigenetic programming in the ovarian reserve

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## Abstract

The ovarian reserve defines female reproductive lifespan, which in humans spans decades. The ovarian reserve consists of oocytes residing in primordial follicles arrested in meiotic prophase I and is maintained independent of DNA replication and cell proliferation, thereby lacking stem cell-based maintenance. Largely unknown is how cellular states of the ovarian reserve are established and maintained for decades. Our recent study revealed that a distinct chromatin state is established during ovarian reserve formation in mice, uncovering a novel window of epigenetic programming in female germline development. We showed that an epigenetic regulator, Polycomb Repressive Complex 1 (PRC1), establishes a repressive chromatin state in perinatal mouse oocytes that is essential for prophase I-arrested oocytes to form the ovarian reserve. Here we discuss the biological roles and mechanisms underlying epigenetic programming in ovarian reserve formation, highlighting current knowledge gaps and emerging research areas in female reproductive biology.

### Keywords

epigenetic programming; epigenetic reprogramming; meiosis; oogenesis; ovarian reserve; Polycomb

## INTRODUCTION

Female germline development requires several key steps to generate mature oocytes ready for fertilization (Figure 1). In mice, primordial germ cell (PGC) precursors first emerge around embryonic day (E) 6.25.[1] After specification and migration to the gonad, PGCs begin rapid proliferation by mitotic cell division with incomplete cytokinesis around E10.75 to form cell clusters known as germline cysts.[2] After epigenetic reprogramming (including genome-wide DNA demethylation) and sex determination, female germ cells enter meiosis beginning E13.5 and become oocytes.[3] Following chromosome pairing and recombination

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during meiotic prophase I (MPI), the resulting oocytes are arrested at the specialized diplotene stage called dictyate around the time of birth; dictyate is from the Greek word diktyon for net because the chromosomes are diffuse. Meanwhile, germline cysts break apart into single oocytes surrounded by pregranulosa cells to form primordial follicles.[4] Because there is a significant loss of oocytes due to programmed cell death during cyst breakdown, only one-third of the initial number of oocytes survive.[5]

In contrast to mammalian males, which replenish their germline throughout life due to spermatogonial stem cells, mammalian females lack a corresponding stem cell population and are born with a finite number of primordial follicles. Non-growing oocytes (NGOs) within these follicles undergo neither DNA replication nor proliferation and constitute the ovarian reserve that determines female reproductive lifespan. The ovarian reserve sustains fertility in mice for months and humans for decades.

During mouse postnatal oogenesis, a selected set of NGOs within primordial follicles enter the growth phase in each estrous cycle, while the vast majority of NGOs remain as the ovarian reserve until they are exhausted; in human females, this depletion results in menopause. The selected oocytes increase in size, known as growing oocytes (GOs), accumulating proteins, RNAs, and organelles that constitute the eggs dowry that supports early embryonic development.[6] Oocyte growth is accompanied by granulosa cell proliferation. When oocytes reach their final size (full-grown oocytes (FGOs)) they resume meiosis I after a gonadotropin surge and are subsequently rearrested at metaphase II, ovulated, awaiting fertilization, which initiates resumption of meiosis and zygote formation.[7]

Extensive epigenetic changes occur during development of PGCs to FGOs.[8] Epigenetic changes in histone modifications and DNA methylation can generate long-lasting chromatin states that define gene expression programs unique to a specific cell type. After epigenetic reprogramming (DNA demethylation) in PGCs, there is an extended period of time, spanning decades in humans, in which oocytes maintain a low level of DNA methylation before various histone modifications and global DNA methylation are eventually established during oocyte growth.[9] Therefore, DNA methylation-independent chromatin-based mechanisms likely operate during such a long period in the female germline. Largely unknown, however, is how the oocyte epigenome is generated when the ovarian reserve is established and then maintained as arrested NGOs within primordial follicles prior to establishment of histone modifications and DNA methylation during oocyte growth. We summarize here the epigenetic reprogramming and programming in female germline development within the context of the most recent advances in the field and highlight newly discovered epigenetic programming that directs ovarian reserve formation.

## Epigenetic reprogramming and programming in female germline development

**Epigenetic reprogramming in PGCs—**Epigenetic reprogramming in PGCs includes genome-wide loss of 5-methylcytosine (DNA demethylation) and chromatin remodeling, which creates a facultative “naive” epigenome in preparation for a sex-specific epigenome. In female PGCs, MPI is initiated through activation of a group of germline genes by DNA demethylation[10] and release from Polycomb-mediated silencing.[11]

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Mammalian Polycomb proteins, which repress transcription of key developmental genes, comprise two functionally-related major complexes—PRC1 and PRC2—that catalyze mono-ubiquitination of H2A at lysine 119 (H2AK119ub) and trimethylation of H3 at lysine 27 (H3K27me3), respectively.[12] In PGCs, both PRC1-mediated H2AK119ub and PRC2-mediated H3K27me3 are required to repress germline genes in hypomethylated PGCs and regulate the timing of sexual differentiation between E11.5 and E13.5.[13–15] Thus, PRC1 and PRC2 are functionally interrelated in the regulation of germline genes to withstand global changes in DNA methylation in PGCs and release from Polycomb silencing is the key step for meiosis entry.

Recent studies unveiled the regulatory mechanism of meiotic entry. Initially, retinoic acid (RA)-induced expression of *Stra8* was postulated to initiate meiosis.[16] A later study revealed that bone morphogenetic protein (BMP) and RA signaling synergically specify female germ cell fate and meiotic entry.[17] Downstream of the BMP signaling, a transcription factor, ZGLP1, activates the oogenic program repressed by Polycomb proteins.[18] Another transcription factor, Meiosin, was discovered to be the initiator of the meiotic program and interacts with STRA8.[19]

**Epigenetic programming in postanal oocyte growth—**After NGOs exit the ovarian reserve, an extensive gain of epigenetic modifications (i.e., epigenetic programming) occurs as oocytes grow. In GOs, global de novo DNA methylation is established based on a transcription-coupled mechanism directed by a histone methyltransferase SETD2 that mediates formation of H3K36me3 during postnatal growth.[9] Another histone mark, H3K4me3, a hallmark of active promoters, is restricted to active promoters in GOs but accumulates as broad domains at both promoters and distal regions in FGOs, displaying a noncanonical distribution pattern that negatively correlates with DNA methylation.[20,21] The maternal H3K4me3 pattern is briefly inherited by zygotes, then reprogrammed to the canonical pattern—sharp peaks at active promoters—at the 2-cell stage.[21]

Like H3K4me3, widespread distal H3K27me3 domains are also found in partially methylated DNA domains (PMDs) in mouse oocytes.[22] Further, maternal H3K27me3 from oocytes functions as the DNA-methylation-independent imprinting mechanism in early mouse embryos.[23] This maternal Polycomb-dependent imprinting is initially established by PRC1-mediated H2AK119ub during oogenesis and then maintained as H3K27me3 during preimplantation development, thereby revealing the PRC1-dependent regulation of PRC2 activities.[24] Whereas maternal H3K27me3 is required for embryogenesis, it is dispensable for oogenesis.[25] In contrast, PRC1-mediated H2AK119ub is required for oogenesis; a deficiency in PRC1 function leads to massive gene derepression, developmental defects in oocytes, and subsequent one-cell arrest after fertilization.[26] Moreover, H2AK119ub and H3K27me3 undergo distinct reprogramming dynamics in early embryos.[24,27]

These observations demonstrate a unique epigenome, including distinct patterns of DNA methylation and histone modifications, is formed during oocyte growth and undergoes extensive reprogramming during preimplantation development. The major remaining questions are how the epigenome in NGOs is established and maintained before these critical events and how it leads to epigenetic programming during oocyte growth.

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## Epigenetic programming in ovarian reserve formation

During the transition from MPI to dictyate arrest, oocytes undergo a dynamic transcriptome change,[28–31] which we termed the perinatal oocyte transition (POT).[32] When a subset of NGOs in primordial follicles are selected to initiate oocyte growth in primary follicles, they undergo another major transcriptional transition, termed primordialto-primary-follicle transition (PPT), which is driven by a set of transcription factors.[33] Thus, NGOs have a unique and active transcriptional program distinct from MPI oocytes or GOs. Recent studies reveal several mechanisms driving POT that include hypoxia-inducible factors in induction and maintenance of NGOs,[28] mechanical stress from surrounding granulosa cells, and extracellular matrix for maintenance of NGOs.[34]

We recently focused on a chromatin-based mechanism of POT driven by PRC1,[32] because DNA methylation is not established at POT and PRC1 regulates germline genes in the absence of DNA methylation.[13] By eliminating PRC1 function after E15, we demonstrated that PRC1 suppresses expression of genes required for MPI to enable ovarian reserve formation; absence of PRC1 activity results in loss of the ovarian reserve, premature ovarian failure, and infertility. Following meiotic entry and driven by the release of MPI genes from Polycomb-mediated silencing, MPI genes are again targeted by PRC1 for suppression during the POT. Thus, PRC1 regulates both the entry and exit from the MPI program in the female germline, with PRC1-dependent chromatin programming preceding the dramatic changes in gene expression that occur during perinatal oogenesis.

By defining a novel window of epigenetic programming in ovarian reserve formation, our study raises new questions about mechanistic interrogations of ovarian reserve formation and maintenance. We raise several such questions below (Figure 2).

## What are the epigenomic landscape and chromatin dynamics during ovarian reserve formation?

Our study established that NGO's epigenetic state is critical for ovarian reserve formation. A simple and obvious question remains: "What is the epigenomic landscape in NGOs?" Our study employed genome-wide chromatin profiling by cleavage under targets and release using nuclease (CUT&RUN) experiments and revealed that H2AK119ub is established on postnatal day 1 (P1), which precedes the transcriptional change at POT observed at P5.[32] Thus, PRC1-directed repressive chromatin states predetermine the transcriptomic change in ovarian reserve formation. Emerging questions include what the landscape of global epigenomic changes at POT is, and when and how the chromatin state required for ovarian reserve formation is established. Although there are a few studies that profiled some histone modifications, for example, H3K4me2/3, H3K36me3, in NGOs using low-input chromatin immunoprecipitation (ChIP),[35,36] the overall epigenomic landscape of ovarian reserve remains poorly defined, mainly because it is difficult to obtain readily oocytes residing in primordial follicles in sufficient numbers to conduct such analyses.

This technical obstacle could be overcome by using mice that express a fluorescent protein in NGOs that could be isolated either manually or by fluorescence-activated cell sorting (FACS) from juvenile female mice. Following removal of associated follicle cells,

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the epigenomic landscape for a battery of histone modifications could be established using sensitive chromatin profiling methods, such as ultra-low-input native ChIP (ULI-nChIP),[37] CUT&RUN,[38] and cleavage under targets and tagmentation (CUT&Tag).[39] Candidate modifications for profiling include Polycomb-mediated repressive markers H2AK119ub and H3K27me3, active enhancer mark H3K27ac, poised enhancer marks H3K4me1/2, retrotransposon and heterochromatin-related repressive mark H3K9me3. These profiling studies would be complemented with a genome-wide determination of chromatin accessibility by low-input assay for transposase-accessible chromatin with sequencing (ATAC-seq),[40] which enables detection of various gene regulatory elements.

The dramatic gene expression change during POT is tightly linked to chromatin remodeling. Chromosome conformation capture (3C)-based methods (e.g., high-throughput chromosome conformation capture (Hi-C)) has revealed that the 3D chromatin structure is complex, dynamic, and has a profound impact on gene expression during development.[41] A single-cell Hi-C analysis has reported that the strength of 3D genome organization becomes weaker during oocyte maturation.[42] A recent study using low-input Hi-C revealed highly dynamic regulation of chromatin architecture in oocytes during fetal PGC specification and postnatal oocyte growth, which is in part regulated by PRC1.[43] In line with this observation, PRC1 polymerizes to mediate chromatin condensation.[44] A Hi-C analysis of perinatal oocytes is a promising direction because it will clarify the 3D chromatin dynamics in epigenetic programming in ovarian reserve formation. Such extensive profiling is required for a mechanistic understanding of NGOs because, in the absence of DNA methylation, combinations of these marks will establish the gene regulatory mechanisms required to maintain NGOs in the ovarian reserve.

## What molecular mechanisms drive epigenetic programming during POT?

Comprehensive chromatin profiling of ovarian reserve will be an essential step toward understanding molecular mechanisms driving ovarian reserve formation. These profiling experiments will form the foundation to address other questions, for example, how the writers and erasers of these marks are regulated transcriptionally and post-transcriptionally so that the epigenetic programming during POT is regulated. Functional studies of various epigenetic regulators (e.g., histone methylases/demethylases, chromatin remodelers) using appropriate genetically modified mouse models will likely elucidate how they regulate epigenetic programming during POT.

Further dissection of PRC1-based mechanisms is also warranted for investigation. PRC1 includes several subcomplexes that have distinct proteins. A group of germline genes is directly regulated by a subcomplex of PRC1, PRC1.6, which contains the transcription factor MAX that suppresses the initiation of meiosis.[45,46] This mechanism operates when global DNA methylation is absent in the preimplantation development.[47] Thus, this mechanism could be involved in the suppression of MPI genes during ovarian reserve formation.

Little is known about the molecular basis for POT, and providing such an understanding will address and answer many questions. For example, what triggers the epigenomic change and chromatin remodeling during POT? Previous studies implicate several critical signaling

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pathways regulating primordial follicle formation,[48,49] for example, KIT signaling,[50] Notch signaling,[51] and PI3K pathway.[52] Could these signaling cues trigger the epigenome events that program gene expression? In addition to cell-intrinsic signaling, cell-extrinsic signaling from granulosa cells are critical in the regulation of oocytes. A promising direction is to examine how cell-intrinsic and -extrinsic signaling regulate epigenetic changes during POT.

Because transcription factors drive key transitions in germ cell development, it is critical to determine how epigenetic changes during POT are driven by transcription factors. Indeed, several oocyte-specific transcription factors, such as FIGLA, NOBOX, and TAF4B, are implicated in ovarian reserve formation,[5] and a transcription factor FOXO3A is implicated in ovarian reserve maintenance.[53] Along a similar vein, in light of hypoxia inducing a "dormant" state in NGOs[28]; oxygen tension could also be linked to establishing and maintaining the correct epigenetic landscape because molecular oxygen is a substrate for histone demethylases such as KDM6A (H3K27me3 demethylase). Hypoxia induces rapid changes in histone methylation (e.g., demethylation of H3K27me3) and chromatin dynamics.[54,55] Therefore, the impact of hypoxia on the epigenetic state of NGOs should be examined in future studies.

Changes in chromatin states provide cellular memories to prepare developmental transitions during germ cell development. Thus, these directions will likely uncover how chromatin states of NGOs predetermine gene expression and epigenetic programming of GOs.

Further, oocyte differentiation and folliculogenesis are genetically dissociable from meiosis in mouse oocytes. This was concluded in genetic experiments showing that *Stra8*-deficient female germ cells grow and differentiate into oocyte-like cells that can be ovulated and fertilized but fail to enter meiosis.[33,56] This uncoupling raises following questions: What is epigenetic regulation's role behind these two dissociable developmental events? Could epigenetic programming take place without meiosis entry? How is chromatin remodeled for differentiation of oocytes in the absence of meiosis? Thus, it will be important to dissect the mechanistic relationship between epigenetic programming and meiosis. Answers to such questions will likely shed light on how oocyte-like cells can be generated in culture without undergoing meiosis.[33]

## What is the effect of age on the epigenome of the ovarian reserve?

Human female fertility declines dramatically in the fourth decade of life because of an age-related decrease in oocyte quality and quantity.[57] Notably, most previous studies about oocyte aging were conducted using FGOs. Whether such changes arise during oocyte growth or are the product of changes in NGOs is not fully resolved. Age-dependent deterioration of cohesin is considered a major cause of a decline in oocyte quality with age.[58] Changes in the chromatin state of the ovarian reserve could be a major contributing factor to the age-dependent decline in oocyte quality. Loss of epigenetic information as a potential cause of aging emerged from yeast studies in the 1990s and was further seen in multicellular organisms that show epigenetic changes (including DNA methylation patterns, H3K4me3, H3K9me3, and H3K27me3) linked to aging. Recently, epigenetic changes underlie mammalian aging as well[59]; erosion of the epigenetic landscape (e.g., H3K27me3,

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H3K27ac) causing loss of ability to maintain cellular identity is associated with aging in mice. Therefore, in the ovarian reserve, degradation of chromatin state during long-term maintenance could be a primary basis for oocyte aging. Thus, it is imperative to determine the epigenomic landscapes in adult ovarian reserve, especially in aged females.

## CONCLUSION

In this review, we present a brief overview of epigenetic programming and reprogramming during female germline development and highlight a newly identified window of epigenetic programming in ovarian reserve formation. In particular, we stress the role of Polycomb-mediated epigenetic programming in POT during ovarian reserve formation and propose that a coordinated complex epigenetic programming system, including various histone modifications and chromatin remodeling, is responsible for the establishment and long-term maintenance of the ovarian reserve. We further pose a series of questions that arise from this proposal with the hope that they will stimulate new avenues of research, the products of which will increase our understanding of the molecular underpinnings of the female germline that, in turn, will increase our understanding of female reproductive longevity.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## Abbreviations:

| | |
|---|---|
| **ATAC-seq** | assay for transposase-accessible chromatin with sequencing |
| **ChIP** | chromatin immunoprecipitation |
| **CUT&RUN** | cleavage under targets and release using nuclease |
| **CUT&Tag** | cleavage under targets and tagmentation |
| **FACS** | fluorescence-activated cell sorting |
| **FGOs** | full-grown oocytes |
| **GOs** | growing oocytes |
| **Hi-C** | high-throughput chromosome conformation capture |
| **MPI** | meiotic prophase I |
| **NGOs** | non-growing oocytes |
| **PGC** | primordial germ cells |

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| | |
|---|---|
| **PMDs** | partially methylated DNA domains |
| **POT** | perinatal oocyte transition |
| **PPT** | primordial-to-primary-follicle transition |
| **PRC** | polycomb repressive complex |

## REFERENCES


1. Hancock GV, Wamaitha SE, Peretz L, & Clark AT (2021). Mammalian primordial germ cell specification. Development, 148, dev189217. [PubMed: 33722957]
2. Spradling AC, Niu W, Yin Q, Pathak M, & Maurya B (2022). Conservation of oocyte development in germline cysts from Drosophila to mouse. Elife, 11, e83230. [PubMed: 36445738]
3. Ramakrishna NB, Murison K, Miska EA, & Leitch HG (2021). Epigenetic regulation during primordial germ cell development and differentiation. Sexual Development, 15, 411–431. [PubMed: 34847550]
4. Grive KJ (2020). Pathways coordinating oocyte attrition and abundance during mammalian ovarian reserve establishment. Molecular Reproduction and Development, 87, 843–856. [PubMed: 32720428]
5. Grive KJ, & Freiman RN (2015). The developmental origins of the mammalian ovarian reserve. Development, 142, 2554–2563. [PubMed: 26243868]
6. Schultz RM, Stein P, & Svoboda P (2018). The oocyte-to-embryo transition in mouse: past, present, and future. Biology of Reproduction, 99, 160–174. [PubMed: 29462259]
7. Viveiros MM, De L, & Fuente R (2019). Chapter 11 – Regulation of mammalian oocyte maturation. In Leung PCK & Adashi EY (Eds.), The ovary (3rd ed., pp. 165–180). Academic Press.
8. Shirane K, & Lorincz M (2023). Epigenetic mechanisms governing female and male germline development in mammals. Sexual Development, 2023, 364–386.
9. Xu Q, Xiang Y, Wang Q, Wang L, Brind'Amour J, Bogutz AB, Zhang Y, Zhang B, Yu G, Xia W, Du Z, Huang C, Ma J, Zheng H, Li Y, Liu C, Walker CL, Jonasch E, Lefebvre L, ... Xie W, (2019). SETD2 regulates the maternal epigenome, genomic imprinting and embryonic development. Nature Genetics, 51, 844–856. [PubMed: 31040401]
10. Hargan-Calvopina J, Taylor S, Cook H, Hu Z, Lee SA, Yen MR, Chiang YS, Chen PY, & Clark AT (2016). Stage-specific demethylation in primordial germ cells safeguards against precocious differentiation. Developmental Cell, 39, 75–86. [PubMed: 27618282]
11. Hill PWS, Leitch HG, Requena CE, Sun Z, Amouroux R, Roman-Trufero M, Borkowska M, Terragni J, Vaisvila R, Linnett S, Bagci H, Dharmalingham G, Haberle V, Lenhard B, Zheng Y, Pradhan S, & Hajkova P (2018). Epigenetic reprogramming enables the transition from primordial germ cell to gonocyte. Nature, 555, 392–396. [PubMed: 29513657]
12. Kim JJ, & Kingston RE (2022). Context-specific Polycomb mechanisms in development. Nature Reviews Genetics, 23, 680–695.
13. Yokobayashi S, Liang CY, Kohler H, Nestorov P, Liu Z, Vidal M, Lohuizen Mv., Roloff TC., & Peters A. (2013). PRC1 coordinates timing of sexual differentiation of female primordial germ cells. Nature, 495, 236–240. [PubMed: 23486062]
14. Lowe MG, Yen MR, Hsu FM, Hosohama L, Hu Z, Chitiashvili T, Hunt TJ, Gorgy I, Bernard M, Wamaitha SE, Chen PY, & Clark AT (2022). EED is required for mouse primordial germ cell differentiation in the embryonic gonad. Developmental Cell, 57, 1482–95. [PubMed: 35679863]
15. Huang TC, Wang YF, Vazquez-Ferrer E, Theofel I, Requena CE, Hanna CW, Kelsey G, & Hajkova P (2021). Sex-specific chromatin remodelling safeguards transcription in germ cells. Nature, 600, 737–742. [PubMed: 34880491]
16. Koubova J, Menke DB, Zhou Q, Capel B, Griswold MD, & Page DC (2006). Retinoic acid regulates sex-specific timing of meiotic initiation in mice. Proceedings of the National Academy of Sciences of the United States of America, 103, 2474–2479. [PubMed: 16461896]

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17. Miyauchi H, Ohta H, Nagaoka S, Nakaki F, Sasaki K, Hayashi K, Yabuta Y, Nakamura T, Yamamoto T, & Saitou M (2017). Bone morphogenetic protein and retinoic acid synergistically specify female germ-cell fate in mice. The EMBO Journal, 36, 3100–3119. [PubMed: 28928204]
18. Nagaoka SI, Nakaki F, Miyauchi H, Nosaka Y, Ohta H, Yabuta Y, Kurimoto K, Hayashi K, Nakamura T, Yamamoto T, & Saitou M (2020). ZGLP1 is a determinant for the oogenic fate in mice. Science, 367, eaaw4115. [PubMed: 32054698]
19. Ishiguro KI, Matsuura K, Tani N, Takeda N, Usuki S, Yamane M, Sugimoto M, Fujimura S, Hosokawa M, Chuma S, Ko MSH, Araki K, & Niwa H (2020). MEIOSIN directs the switch from mitosis to meiosis in mammalian germ cells. Developmental Cell, 52, 429–445.e10. [PubMed: 32032549]
20. Dahl JA, Jung I, Aanes H, Greggains GD, Manaf A, Lerdrup M, Li G, Kuan S, Li B, Lee AY, Preissl S, Jermstad I, Haugen MH, Suganthan R, Bjørås M, Hansen K, Dalen KT, Fedorcsak P, Ren B, & Klungland A (2016). Broad histone H3K4me3 domains in mouse oocytes modulate maternal-to-zygotic transition. Nature, 537, 548–552. [PubMed: 27626377]
21. Zhang B, Zheng H, Huang B, Li W, Xiang Y, Peng X, Ming J, Wu X, Zhang Y, Xu Q, Liu W, Kou X, Zhao Y, He W, Li C, Chen B, Li Y, Wang Q, Ma J, ... Xie W, (2016). Allelic reprogramming of the histone modification H3K4me3 in early mammalian development. Nature, 537, 553–557. [PubMed: 27626382]
22. Liu X, Wang C, Liu W, Li J, Li C, Kou X, Chen J, Zhao Y, Gao H, Wang H, Zhang Y, Gao Y, & Gao S (2016). Distinct features of H3K4me3 and H3K27me3 chromatin domains in pre-implantation embryos. Nature, 537, 558–562. [PubMed: 27626379]
23. Inoue A, Jiang L, Lu F, Suzuki T, & Zhang Y (2017). Maternal H3K27me3 controls DNA methylation-independent imprinting. Nature, 547, 419–424. [PubMed: 28723896]
24. Mei H, Kozuka C, Hayashi R, Kumon M, Koseki H, & Inoue A (2021). H2AK119ub1 guides maternal inheritance and zygotic deposition of H3K27me3 in mouse embryos. Nature Genetics, 53, 539–550. [PubMed: 33821003]
25. Inoue A, Chen Z, Yin Q, & Zhang Y (2018). Maternal Eed knockout causes loss of H3K27me3 imprinting and random X inactivation in the extraembryonic cells. Genes & Development, 32, 1525–1536. [PubMed: 30463900]
26. Posfai E, Kunzmann R, Brochard V, Salvaing J, Cabuy E, Roloff TC, Liu Z, Tardat M, van Lohuizen M, Vidal M, Beaujean N, & Peters AH (2012). Polycomb function during oogenesis is required for mouse embryonic development. Genes & Development, 26, 920–932. [PubMed: 22499591]
27. Chen Z, Djekidel MN, & Zhang Y (2021). Distinct dynamics and functions of H2AK119ub1 and H3K27me3 in mouse preimplantation embryos. Nature Genetics, 53, 551–563. [PubMed: 33821005]
28. Shimamoto S, Nishimura Y, Nagamatsu G, Hamada N, Kita H, Hikabe O, Hamazaki N, & Hayashi K (2019). Hypoxia induces the dormant state in oocytes through expression of Foxo3. Proceedings of the National Academy of Sciences of the United States of America, 116, 12321–12326. [PubMed: 31147464]
29. Niu W, & Spradling AC (2022). Mouse oocytes develop in cysts with the help of nurse cells. Cell, 185, 2576–90. [PubMed: 35623357]
30. Niu W, & Spradling AC (2020). Two distinct pathways of pregranulosa cell differentiation support follicle formation in the mouse ovary. Proceedings of the National Academy of Sciences of the United States of America, 117, 20015–20026. [PubMed: 32759216]
31. Wang JJ, Ge W, Zhai QY, Liu JC, Sun XW, Liu WX, Li L, Lei CZ, Dyce PW, De Felici M, & Shen W (2020). Single-cell transcriptome landscape of ovarian cells during primordial follicle assembly in mice. PLOS Biology, 18, e3001025. [PubMed: 33351795]
32. Hu M, Yeh YH, Munakata Y, Abe H, Sakashita A, Maezawa S, Vidal M, Koseki H, Hunter N, Schultz RM, & Namekawa SH (2022). PRC1-mediated epigenetic programming is required to generate the ovarian reserve. Nature Communications, 13, 4510.
33. Hamazaki N, Kyogoku H, Araki H, Miura F, Horikawa C, Hamada N, Shimamoto S, Hikabe O, Nakashima K, Kitajima TS, Ito T, Leitch HG, & Hayashi K (2021). Reconstitution of the oocyte transcriptional network with transcription factors. Nature, 589, 264–269. [PubMed: 33328630]

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34. Nagamatsu G, Shimamoto S, Hamazaki N, Nishimura Y, & Hayashi K (2019). Mechanical stress accompanied with nuclear rotation is involved in the dormant state of mouse oocytes. Science Advances, 5, eaav9960. [PubMed: 31249869]
35. Hanna CW, Taudt A, Huang J, Gahurova L, Kranz A, Andrews S, Dean W, Stewart AF, Colomé-Tatché M, & Kelsey G (2018). MLL2 conveys transcription-independent H3K4 trimethylation in oocytes. Nature Structural & Molecular Biology, 25, 73–82.
36. Stewart KR, Veselovska L, Kim J, Huang J, Saadeh H, Tomizawa S, Smallwood SA, Chen T, & Kelsey G (2015). Dynamic changes in histone modifications precede de novo DNA methylation in oocytes. Genes & Development, 29, 2449–2462. [PubMed: 26584620]
37. Brind'Amour J, Liu S, Hudson M, Chen C, Karimi MM, & Lorincz MC (2015). An ultra-low-input native ChIP-seq protocol for genome-wide profiling of rare cell populations. Nature Communications, 6, 6033.
38. Skene PJ, Henikoff JG, & Henikoff S (2018). Targeted in situ genome-wide profiling with high efficiency for low cell numbers. Nature Protocols, 13, 1006–1019. [PubMed: 29651053]
39. Kaya-Okur HS, Janssens DH, Henikoff JG, Ahmad K, & Henikoff S (2020). Efficient low-cost chromatin profiling with CUT&Tag. Nature Protocols, 15, 3264–83. [PubMed: 32913232]
40. Grandi FC, Modi H, Kampman L, & Corces MR (2022). Chromatin accessibility profiling by ATAC-seq. Nature Protocols, 17, 1518–1552. [PubMed: 35478247]
41. Zheng H, & Xie W (2019). The role of 3D genome organization in development and cell differentiation. Nature Reviews Molecular Cell Biology, 20, 535–550. [PubMed: 31197269]
42. Flyamer IM, Gassler J, Imakaev M, Brandao HB, Ulianov SV, Abdennur N, Razin SV, Mirny LA, & Tachibana-Konwalski K (2017). Single-nucleus Hi-C reveals unique chromatin reorganization at oocyte-to-zygote transition. Nature, 544, 110–114. [PubMed: 28355183]
43. Du Z, Zheng H, Kawamura YK, Zhang K, Gassler J, Powell S, Xu Q, Lin Z, Xu K, Zhou Q, Ozonov EA, Véron N, Huang B, Li L, Yu G, Liu L, Au Yeung WK, Wang P, Chang L, ... Xie W, (2020). Polycomb group proteins regulate chromatin architecture in mouse oocytes and early embryos. Molecular Cell, 77, 825–39. [PubMed: 31837995]
44. Isono K, Endo TA, Ku M, Yamada D, Suzuki R, Sharif J, Ishikura T, Toyoda T, Bernstein BE, & Koseki H (2013). SAM domain polymerization links subnuclear clustering of PRC1 to gene silencing. Developmental Cell, 26, 565–577. [PubMed: 24091011]
45. Endoh M, Endo TA, Shinga J, Hayashi K, Farcas A, Ma KW, Ito S, Sharif J, Endoh T, Onaga N, Nakayama M, Ishikura T, Masui O, Kessler BM, Suda T, Ohara O, Okuda A, Klose R, & Koseki H (2017). PCGF6-PRC1 suppresses premature differentiation of mouse embryonic stem cells by regulating germ cell-related genes. Elife, 6, e21064. [PubMed: 28304275]
46. Suzuki A, Hirasaki M, Hishida T, Wu J, Okamura D, Ueda A, Nishimoto M, Nakachi Y, Mizuno Y, Okazaki Y, Matsui Y, Izpisua Belmonte JC, & Okuda A (2016). Loss of MAX results in meiotic entry in mouse embryonic and germline stem cells. Nature Communications, 7, 11056.
47. Mochizuki K, Sharif J, Shirane K, Uranishi K, Bogutz AB, Janssen SM, Suzuki A, Okuda A, Koseki H, & Lorincz MC (2021). Repression of germline genes by PRC1.6 and SETDB1 in the early embryo precedes DNA methylation-mediated silencing. Nature Communications, 12, 7020.
48. Wang C, Zhou B, & Xia G (2017). Mechanisms controlling germline cyst breakdown and primordial follicle formation. Cellular and Molecular Life Sciences, 74, 2547–2566. [PubMed: 28197668]
49. O'Connell JM, & Pepling ME (2021). Primordial Follicle Formation – Some Assembly Required. Current Opinion in Endocrine and Metabolic Research, 18, 118–127. [PubMed: 34027225]
50. Jones RL, & Pepling ME (2013). KIT signaling regulates primordial follicle formation in the neonatal mouse ovary. Developmental Biology, 382, 186–197. [PubMed: 23831378]
51. Xu J, & Gridley T (2013). Notch2 is required in somatic cells for breakdown of ovarian germ-cell nests and formation of primordial follicles. BMC Biology, 11, 13. [PubMed: 23406467]
52. Burton JJN, Luke AJ, & Pepling ME (2022). Regulation of mouse primordial follicle formation by signaling through the PI3K pathway. Biology of Reproduction, 106, 515–525. [PubMed: 34725674]

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53. Castrillon DH, Miao L, Kollipara R, Horner JW, & DePinho RA (2003). Suppression of ovarian follicle activation in mice by the transcription factor Foxo3a. Science, 301, 215–218. [PubMed: 12855809]

54. Batie M, Frost J, Frost M, Wilson JW, Schofield P, & Rocha S (2019). Hypoxia induces rapid changes to histone methylation and reprograms chromatin. Science, 363, 1222–1226. [PubMed: 30872526]

55. Chakraborty AA, Laukka T, Myllykoski M, Ringel AE, Booker MA, Tolstorukov MY, Meng YJ, Meier SR, Jennings RB, Creech AL, Herbert ZT, McBrayer SK, Olenchock BA, Jaffe JD, Haigis MC, Beroukhim R, Signoretti S, Koivunen P, & Kaelin WG Jr (2019). Histone demethylase KDM6A directly senses oxygen to control chromatin and cell fate. Science, 363, 1217–1222. [PubMed: 30872525]

56. Dokshin GA, Baltus AE, Eppig JJ, & Page DC (2013). Oocyte differentiation is genetically dissociable from meiosis in mice. Nature Genetics, 45, 877–883. [PubMed: 23770609]

57. Hunter N (2017). Oocyte quality control: Causes, mechanisms, and consequences. Cold Spring Harbor Symposia on Quantitative Biology, 82, 235–247. [PubMed: 29743337]

58. Chiang T, Duncan FE, Schindler K, Schultz RM, & Lampson MA (2010). Evidence that weakened centromere cohesion is a leading cause of age-related aneuploidy in oocytes. Current Biology, 20, 1522–1528. [PubMed: 20817534]

59. Yang JH, Hayano M, Griffin PT, Amorim JA, Bonkowski MS, Apostolides JK, Salfati EL, Blanchette M, Munding EM, Bhakta M, Chew YC, Guo W, Yang X, Maybury-Lewis S, Tian X, Ross JM, Coppotelli G, Meer MV, Rogers-Hammond R, ... Sinclair DA. (2023). Loss of epigenetic information as a cause of mammalian aging. Cell, 186, 305–26. [PubMed: 36638792]

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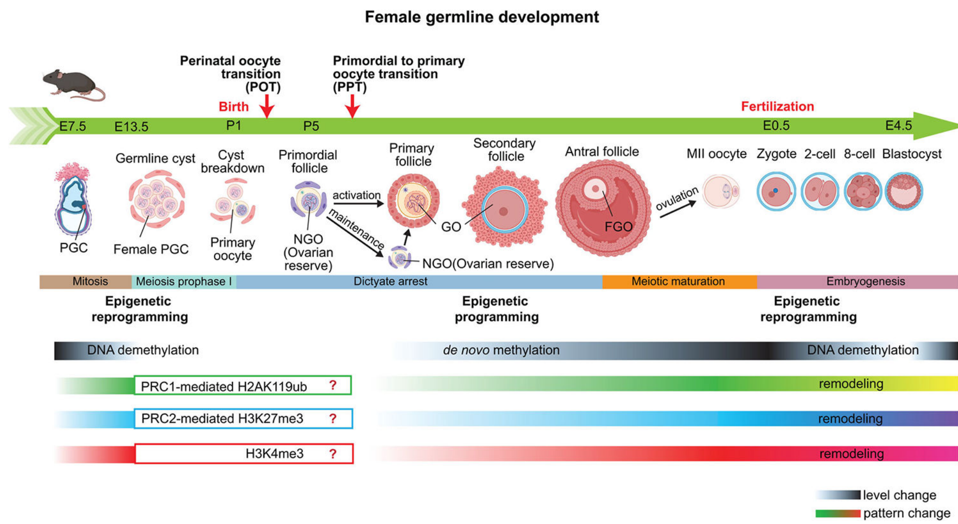


**FIGURE 1.**

Scheme of female germline development. The developmental process of mouse germ cells is depicted (created with BioRender.com). Key events in epigenome reprogramming and/or programming are listed. DNA methylation levels and common histone modifications are represented with a graph. Blank regions and question marks show unexplored stages. PGC, primordial germ cells; NGO, non-growing oocyte; GO, growing oocyte; FGO, full-grown oocyte; MII, metaphase II.

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**FIGURE 2.**

Scheme of ovarian reserve formation. Key cellular events that occurred during the ovarian reserve formation are listed, and the proposed epigenetic programming and chromatin remodeling in the nucleus are depicted (created with BioRender.com). Question marks point out unresolved questions or unclear mechanisms.