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# Asymmetric inheritance of parental histones leads to differentiation defects in mouse embryonic stem cells

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Since the discovery of DNA as the genetic material in 1944, significant progress has been made in understanding how genetic information is transferred from parent to daughter cells through DNA replication processes. We now know that epigenetic inheritance is fundamental to the establishment and maintenance of cell lineages and also plays a pivotal role in determining cell fate. Epigenetic inheritance is characterized by heritable differences in gene expression independent of differences in genomic information. In eukaryotic cells, the transfer of epigenetic information is also tightly linked to genome replication, via the transmission of chromatin structure from parent to daughter cells.

Despite ongoing researches into the mechanisms of epigenetic inheritance, a significant knowledge gap persists regarding the particular mechanisms by which chromatin structure is inherited during DNA replication. Nucleosome assembly is the initial step in the transfer of epigenetic information from parent to daughter cells. As the replication fork progresses, the nucleosomes are disassembled to facilitate the passage of the replisome. After DNA replication cation is completed, the two newly synthesized DNA daughter strands inherit the parental histones from the original strand and recruit newly synthesized histones to maintain consistent nucleosome structure. The faithful transfer and restoration of post-translational histone modifications reflective of parental histone states are critical for maintaining cell identity throughout cellular replication. Given the defining nature of histone modifications on epigenetic states, what effects could the disruption of parental histone transfer then have on cellular differentiation and the overall development of organisms? In this commentary, we describe the results of a recent study by Wen et al. that links the parental histone transfer process to cellular differentiation of mouse embryonic stem cells (mESCs). [1]



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DECLARATION OF INTERESTS

The authors declare no competing interests.

## LINKING PARENTAL HISTONE TRANSFER TO CELL DIFFERENTIATION AND mESC

Recently, researchers developed a method called eSPAN (Enrichment and Sequencing of Protein-Associated Nascent DNA) to study the process of DNA replication-coupled nucleosome assembly.[2] Using eSPAN, they revealed the roles of the Pole3/4 and Mcm2-Ctf4-Polα axis in transferring parental histones with their corresponding epigenetic modifications to the leading and lagging strands of the DNA replication fork in budding yeast. In general, parental histone transfer is performed nearly symmetrically between the two replication strands. However, this balance can be intentionally disrupted through the mutation of Pole3/4 or Mcm2. Based on these findings, a fundamental question arises: could biased distribution of epigenetic information following DNA replication lead to daughter cells with different epigenetic landscapes? This question holds great importance as different epigenetic landscapes result in differences in gene expression and other cellular properties. A biased inheritance leading to different epigenomes would underscore the critical role of parental nucleosome assembly in the growth and development of multicellular organisms.

To answer this question, Wen et al. from the Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences (SIAT) conducted a comprehensive study using mESCs as a model.[1] The results of Wen et al. and those of Wenger et al. indicate that symmetric inheritance and uniform distribution of parental histones are critical for maintaining specific cell fates and promoting normal neuronal differentiation of mESCs during embryonic development.[1,3] These studies demonstrate that biased distribution of parental histones leads to several outcomes: (1) epigenetic heterogeneity; (2) variability in gene expression; (3) defects in mESC differentiation along the neuronal lineage, leading to the formation of superclones; and (4) impaired pre-implantation development at the four-cell stage, ultimately reducing the efficacy of morula development and resulting in mouse embryonic lethality ( Figure 1).

## IMPACT OF PARENTAL HISTONE INHERITANCE ON mESC DIFFERENTIATION

To investigate the possible role of parental histone assignment in mESC differentiation, the researchers developed mESC models with mutations that impair histone chaperone function: both an Mcm2–2A mutant and a Pole3 knockout (KO) mutant. The Mcm2–2A mutation resulted in a defect in the binding and transferring of parental histones to the lagging strand during replication, whereas the Pole3 KO resulted in a defect in the transfer of parental histones to the leading strand (Figure 1).

To investigate how the asymmetric distribution of parental histones during DNA replication affects mESC differentiation, Wen et al.[1] performed various assays, including single-cell histone modification CUT&Tag, single-cell RNA-seq (scRNA-seq), and LARRYbarcode profiling (which utilizes a barcoding system detectable by scRNA-seq and is used for clonal lineage labeling). These assays allowed them to trace epigenomic and transcriptomic changes in Mcm2–2A mutant cells throughout the differentiation process. Abnormal

genome-wide distribution patterns were noted for key histone marks such as H3K27me3, H3K9me3, and H3K4me3. Wen et al. focused on the patterning of H3K27me3, which is closely associated with cell differentiation and multicellular development. They found that the Mcm2–2A mutant mESCs had a tendency to differentiate into all three embryonic layers rather than the expected result of primarily neuronal cells as seen in WT mESCs. During the mutant ESC differentiation process, the heterogeneity of H3K27me3 distribution increased among the progeny, as did the heterogeneity of the transcriptome. Furthermore, the expression levels of development-related genes were negatively correlated with H3K27me3 peak heights, and changes in the activation of neuronal lineage genes was observed compared to WT. Taken together, these results suggest that parental histone distribution contributes significantly to shaping chromatin states during cell differentiation and ultimately regulates the differentiation potential of ESCs.

In addition to histone methylation modifications, Wen et al. discovered that the parental inheritance process may also regulate mESC differentiation, possibly through the assembly of histone H3 variants. Previous studies have suggested the histone variant H3.3 plays a role in establishing the correct H3K27me3 patterns at the promoters of bivalent genes in mESCs. Intriguingly, Wen et al. found that H3.3 exhibited a leading strand preference in Mcm2–2A mutant mESCs and a pronounced lagging strand bias in Pole3 KO mESCs.[1] It is likely that the changes in the H3K27me3 distribution between Mcm2–2A mutant and WT are influenced by histone H3.3 changes. Furthermore, the increased H3K27me3 heterogeneity in the mutant likely contributes to the variation in gene expression and aberrant cell differentiation. In other words, biased parental histone allocation affects not only the distribution of histone modifications but also the localization of histone variants, ultimately affecting the epigenome. This, in turn, increases epigenetic and transcriptional heterogeneity within the daughter cell populations, thereby altering their cellular fate.

It is noteworthy that Wen et al. found that MCM2–2A mutant mESCs, despite their altered differentiation potential, maintained normal proliferation with no apparent effects on the cell cycle.[1] This suggests two key points for further consideration. (1) Epigenetic modifications are more important in driving changes in cell fate than in maintaining cell stability. ESC proliferation appears to be insensitive to the epigenetic changes targeted in this study. It is plausible that the role of targeted histone modifications during ESC proliferation is over-shadowed by the influence of other regulatory factors such as transcription factors or other epigenetic modifications. (2) A cleaner model system, such as budding yeast, may make it easier to uncover the essential roles of individual epigenetic modifications, as an example, the *de novo* synthesis of DNA 5mC to reveal its influence on the structure and function of chromatin.[4]

## IMPACT OF PARENTAL HISTONE INHERITANCE ON MOUSE DEVELOPMENT AND BEYOND

Wen et al. also generated Mcm2–2A mutant mice. As expected, homozygous Mcm2–2A mice exhibit early embryonic developmental defects and embryonic lethality. Based on these findings, the researchers concluded that the symmetric distribution and inheritance

of parental histones plays a crucial role in early embryonic development. Given the fundamental role of cellular differentiation and development in the survival of multicellular organisms, it is reasonable to anticipate that nucleosome assembly plays a widespread role in the differentiation of many different phyla. Asymmetric cell division is sometimes required to establish and maintain distinct gene expression programs in different cell lineages during the development of multicellular organisms. For example, the disruption of asymmetric distribution of parental histones in *Drosophila* germline stem cells has been linked to the onset of early germline tumors and the loss of germline stem cells.[5] These results suggest that histone modification bias due to histone distribution asymmetry could have significance biological significance. To further investigate the influence of the nucleosome assembly pathway on cellular differentiation and development, more extensive studies in diverse multicellular organisms are crucial.

## SUMMARY AND FUTURE RESEARCH DIRECTIONS

In conclusion, the work of Wen et al. and Wenger et al.[1,3] has demonstrated the importance of a symmetrical distribution of parental histones onto the newly generated chromatin of the daughter cells during DNA replication. This discovery establishes that the symmetric transmission of post-translational histone modifications between each DNA replication strand is a fundamental feature of cellular differentiation and development. The groundbreaking work of Wen et al. and Wenger et al.[1,3] also highlights the importance of parental histone inheritance in perpetuating histone modification landscapes, which in turn, plays a crucial role in mESC differentiation and early mouse embryonic development (Figure 1). Such findings are of profound scientific importance and enhance our understanding of the inheritance of epigenetic information in daughter cells during cell division.

The work of Wen et al. also raises several interesting follow-up questions. First, it prompts us to investigate why parental histone allocation does not have a significant impact on the cell cycle. Second, it beckons us to investigate how different chromatin structures are inherited from parent cells to daughter cells. Finally, it leads us to contemplate whether the disruption of the symmetrical distribution of parental histones could induce changes in higher-order chromatin architecture and in the interactions between promoters and enhancers in daughter cells. Given the broad impact of these findings, we anticipate further insights into chromatin replication mechanisms within this field.

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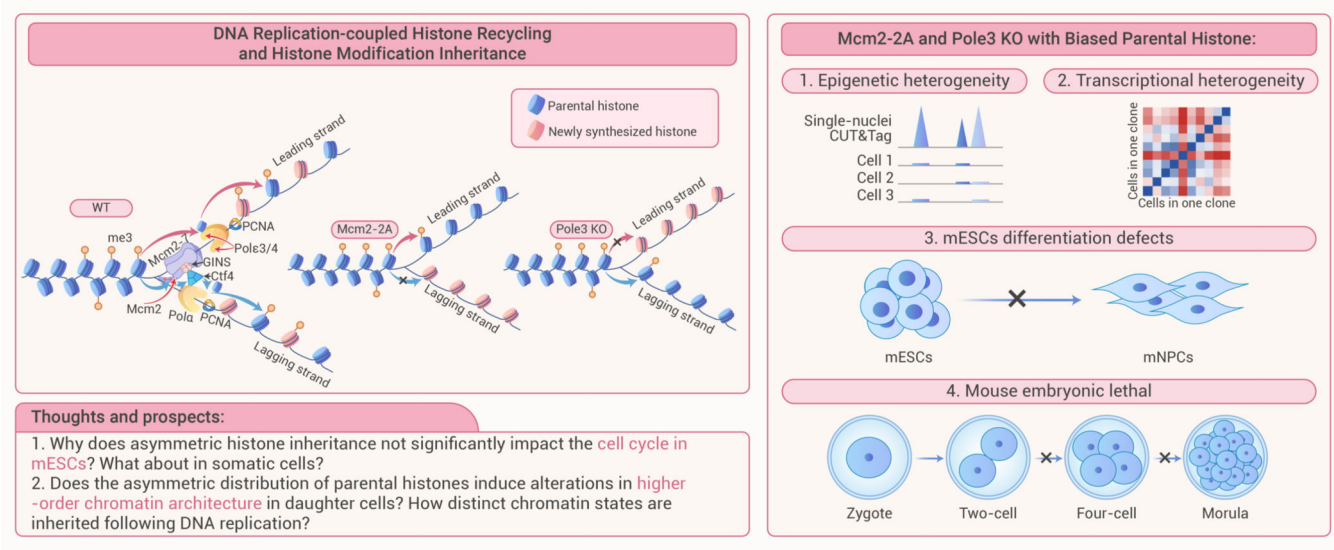


**Figure 1.**

Schematic representing asymmetric inheritance of parental histones in DNA replication as a result of the mutation of Mcm2–2A or the deletion of Pole3, and the resulting functional and differentiation defects in mouse embryonic stem cells (mESCs).