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Safeguarding the epigenome through the cell cycle: a multitasking game

Valentin Flury[1,2,#] and Anja Groth[1,2,3,*,#]

Sustaining cell identity and function across cell division is germane to human development, healthspan, and cancer avoidance. This relies significantly on propagation of chromatin organization between cell generations, as chromatin presents a barrier to cell fate and cell state conversions. Inheritance of chromatin states across the many cell divisions required for development and tissue homeostasis represents a major challenge, especially because chromatin is disrupted to allow passage of the DNA replication fork to synthesize the two daughter strands. This process also leads to a twofold dilution of epigenetic information in histones, which needs to be accurately restored for faithful propagation of chromatin states across cell divisions. Recent research has identified distinct multilayered mechanisms acting to propagate epigenetic information to daughter strands. Here, we summarize key principles of how epigenetic information in parental histones is transferred across DNA replication and how new histones robustly acquire the same information postreplication, representing a core component of epigenetic cell memory.

Addresses
[1] Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, 2200 Copenhagen, Denmark
[2] Biotech Research and Innovation Centre, University of Copenhagen, 2200 Copenhagen, Denmark
[3] Department of Cellular and Molecular Medicine, University of Copenhagen, 2200 Copenhagen, Denmark

Corresponding author: Groth, Anja (anja.groth@cpr.ku.dk)
[*] Postal address: building 6.3, Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark.
[#] Twitter account: @ValeFlury, @groth_anja

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Epigenetic memory across scales

Epigenetic memory enables cells to maintain gene expression programs across time and record their past experiences by converting transient perturbations, such as differentiation signals and environmental input into heritable changes. This provides cellular robustness during development and protection against unwarranted cell fate changes associated with cancer. A fundamental component of epigenetic memory are chemical modifications that decorate DNA itself or its basic packaging units, the nucleosomes. These modifications repress expression of harmful transposable elements, ensure faithful DNA repair, and finetune gene expression programs, thereby promoting genome stability and counteracting cell malfunction. Hence, faithful maintenance of epigenetic information across cell division is of major importance to cell functionality, serving as a barrier to aging and disease [1–3].

Epigenetic memory can be understood at various scales, ranging from inter- and transgenerational epigenetic inheritance between organismal generations (see review by Fitz-James and Cavalli [4]) to memory across cell division within an organism. This review discusses epigenetic cell memory that addresses how epigenetic information is propagated to daughter cells during cell division. We will focus on histone modifications and how they are inherited to daughter cells, a process that when impaired obscures cell identity and impairs differentiation *in vitro* and *in vivo* [5,6]. We will showcase the mechanisms ensuring accurate transmission of histone-based information during DNA replication and how they template modification of new histones. We refer to other reviews for a discussion of transmission of epigenetic information by mitotic bookmarking [7] and DNA methylation maintenance [8].

Inheritance of histone-based information across the cell cycle

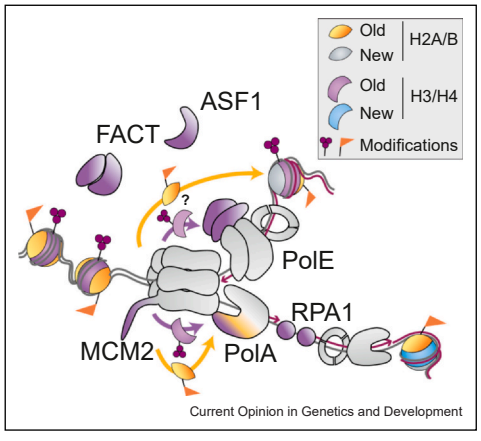
During DNA replication, chromatin is disrupted ahead of the replication fork to allow synthesis of the two daughter strands. In the wake of replication, daughter DNA strands are assembled into nucleosomes using old histones recycled from the parental strand and newly synthesized (naïve) histones. The doubling of DNA necessitates deposition of naïve histones in numbers matching old histones, and — as they are largely

unmodified — all parental histone modifications are diluted at least twofold. Consequently, correct histone modifications must be imposed on naïve histones to maintain the chromatin landscape across cell division and counteract loss of epigenetic information during subsequent rounds of replication. Broadly, propagation of histone-based information can be separated into three types of processes: (a) transfer of modified parental histones during replication fork passage, maintaining positional information; (b) reassembly of nucleosomes on replicated DNA through a combination of old recycled and newly synthesized histones; and (c) feedback-driven restoration of the histone modification landscape templated by parental information or more DNA sequence-dependent restoration driven by processes such as transcription [9,10].

Transfer of epigenetic information during DNA replication fork passage

Replication of genetic information is directly coupled to the propagation of epigenetic information in histones, thereby laying the foundation for epigenetic memory. The discovery that the replicative helicase, via its MCM2 subunit, acts as a histone chaperone transferring parental histones H3-H4 as well as H3.3 and CENP-A variants with their epigenetic modifications to daughter strands paved the way for this paradigm [11–16]. Several core components of the replication fork, including PolE3/E4 [17,18] and PolA1 [19–21], have now been identified to contain histone-binding properties and guide parental histones to leading and lagging strands (Figure 1). In addition to replisome factors, dedicated histones chaperones, such as Anti-Silencing Factor 1 (ASF1) and FAcilitates Chromatin Transcription (FACT), aid the transfer of histones to daughter strands, forming co-chaperone complexes with replisome components to shield parental histones from nonspecific interactions (reviewed in Ref. [22]) and likely facilitate their movement across the replisome. While ASF1 recruitment is mediated by histones in transfer, FACT interacts with multiple subunits of the replication machinery, ranging from the front of the fork (Tof1/Timeless [23]) across the core (MCM2/4 [24]) to lagging strand components (PolA1, RPA1) behind the fork (reviewed in Ref. [25]). Hence, each parental H3-H4 tetramer might be bound by one FACT heterodimer to form a ternary complex [24] that engages with several contact points across the replisome via co-chaperone interactions until ultimately depositing H3-H4 tetramers on daughter strands; this would nicely parallel a recent study of how FACT transfers histones during RNA Polymerase II elongation [26]. However, this remains speculative, and much remains to be learned about how movement of histones is co-ordinated and integrated with progression of the fork.

Figure 1



Transfer of histones with their modification across the DNA replication fork. Components of the replication fork with demonstrated histone interaction and histone chaperones acting at the replication fork are shown in the respective color (purple for H3-H4 recycling and yellow for H2A-H2B recycling). Modifications on histones represented as circles (H3-H4) or flags (H2A-H2B), respectively.

Histones H2A-H2B were recently found also to be recycled symmetrically to both strands in a manner that maintains positional information [21]. However, a distinct recycling mechanism appears to be involved, as H2A-H2B was recycled symmetric in MCM2 and POLE3/4 H3-H4 histone recycling mutants [21]. However, mutation of the histone-binding domain in POLA1 skewed H2A-H2B recycling to the leading strand, arguing that this histone binding platform is part of both H3-H4 and H2A-H2B recycling pathways. The existence of parallel pathways to transfer histone H2A-H2B and H3-H4 could ensure robustness in propagation of epigenetic information. Importantly, all active and repressive histone modifications examined on new DNA in yeast and mamalian cells, including the bulky ubiquitination moiety, are recycled with high accuracy, meaning that the modified parental histone is reincorporated within about 250 bp of the original position [21,27–29]. These modifications are present in nascent chromatin (10 min or less after fork passage) and have been confirmed by various assays to stem from histone recycling rather than being imposed *de novo* postreplication; they show strand asymmetry in mamalian and yeast histone recycling mutants [5,6,21,30,31], and they persist despite inhibition of *de novo* modification postreplication both for endogenous modifications [21,27,31] and ectopically induced modifications [28,29,32]. Also histone variants are accurately recycled to both daughter strands, as shown for the variants H3.3 [33] and H2A.Z [21]. Furthermore, a study preventing naïve histone deposition in Drosophila embryos recapitulates accurate histone reoccupancy postreplication for H3-H4 and H2A-H2B modifications, although with more limited time resolution [34]. Thus, nondiscriminating, conserved mechanisms ensure accurate histone recycling to both daughter strands. The full

orchestration of this remains to be identified, especially for H2A-H2B, and potential context- or signaling-dependent regulation of these components to modulate recycling accuracy and symmetry requires investigation (discussed in Ref. [35]). Future studies should also address whether histones are indeed recycled in an alternating manner to leading and lagging strand to ensure maximum symmetry at each genomic loci.

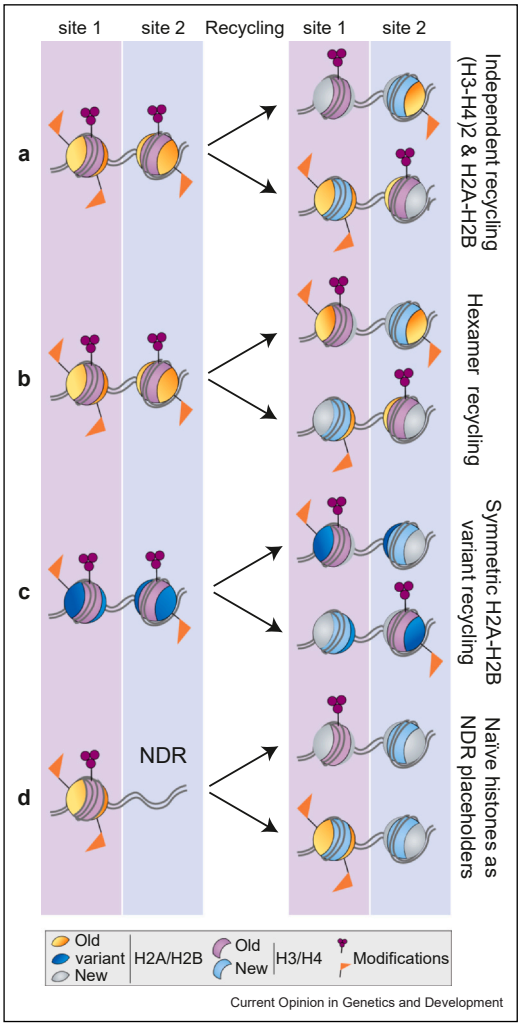
Reassembly of nucleosomes on replicated DNA

The concerted actions of histone chaperones and replication fork components ensure accurate transfer of epigenetic information in parental nucleosomes to both daughter strands. However, the duplication of DNA strands also requires deposition of naïve histones to maintain nucleosome density. Importantly, these naïve histones lack epigenetic information and are highly acetylated (reviewed in Ref. [36]), thereby posing a challenge to the faithful propagation of the parental epigenetic state. A solution to this dilemma is to mix parental histones with naïve ones. Indeed, pioneering work demonstrated that nucleosomes are not recycled as one octameric unit but handled as one $(H3\text{-}H4)_2$ tetramer and two H2A-H2B dimers (reviewed in Ref. [36]). This also means that parental $(H3\text{-}H4)_2$ recycling is not symmetric at the scale of individual nucleosomes, as the entire unit is transferred to either the leading or the lagging strand at a given location. This argues against the robust epigenetic memory of small chromatin domains of just a few nucleosomes in yeast and plants, which thus cannot be explained by epigenetic memory acting via H3-H4 alone [37–40].

The finding that H2A-H2B are also recycled and by a distinct mechanism has major consequences for the reassembly of new nucleosomes on daughter strands as it amplifies the likelihood of transferring epigenetic information to all reassembled nucleosomes on daughter strands (Figure 2). Deposition of parental and naïve H2A-H2B dimers occur after assembly of $(H3\text{-}H4)_2$ into tetrasomes, thus likely enabling naïve H3-H4 to be mixed with parental H2A-H2B and vice versa (Figure 2a). This 'mix'n'match' approach would increase the likelihood of transferring epigenetic information to all nucleosomes on nascent chromatin since the two parental H2A-H2B dimers can contribute to nucleosomes on both daughter strands and are recycled independently from $(H3\text{-}H4)_2$. Moreover, it is intriguing to envision that the 'mix'n'match' approach is coordinated such that parental H2A-H2B are mainly deposited with naïve H3-H4 tetramers, but this remains to be tested. Although H2A-H2B recycling remains symmetric in H3-H4 recycling mutants, this does not formally exclude a hexamer model where parental $(H3\text{-}H4)_2$ are recycled with one parental H2A-H2B dimer during replisome passage, a configuration that would parallel RNA polymerase passage [26]. In such scenario, hexamer recycling to one strand could be co-ordinated by transmission of the remaining H2A-H2B dimer to the other strand, which would mitigate fully naïve nucleosomes (Figure 2b).

Recycling of two H2A-H2B dimers also allows the transfer of H2A/H2B variants to both daughter strands during DNA replication. In such case, parental, homotypic nucleosomes could get disrupted ahead of the fork and reassembled as heterotypic nucleosomes on nascent chromatin, thereby providing one variant dimer with

Figure 2



Principles of nucleosome assembly on the two daughter strands after DNA replication (dividing arrows). **(a)** Separate recycling and assembly of a $(H3\text{-}H4)_2$ tetramer and two (H2A-H2B) dimers. **(b)** Hexamer model of $(H3\text{-}H4)_2$(H2A-H2B) resulting in one (H2A-H2B) on the other strand. **(c)** Recycling of homotypic histone H2A variant (blue) nucleosomes resulting in heterotypic nucleosomes on both strands. **(d)** Nucleosome assembly at NDRs.

epigenetic information to both daughter strands (Figure 2c). Indeed, previous research demonstrated that homotypic H2A.Z-containing nucleosomes are mainly present in G1 phase and get converted into heterotypic nucleosomes in S and G2/M [41]. This could have direct functional consequences, as H2A.Z can act as a placeholder, preventing promoters from being prematurely inactivated in early stages of development [42–44]. Thus, a similar model could act on nascent chromatin, where H2A.Z-marked heterotypic nucleosomes may provide an entry site for transcription restart and maintenance of active chromatin after each round of replication. Whether this is important for facilitated promoter clearance postreplication remains unknown. In addition, how other variants such as H2A.X and macroH2A are handled during DNA replication remains unclear, despite their important roles in DNA repair and heterochromatin maintenance [45].

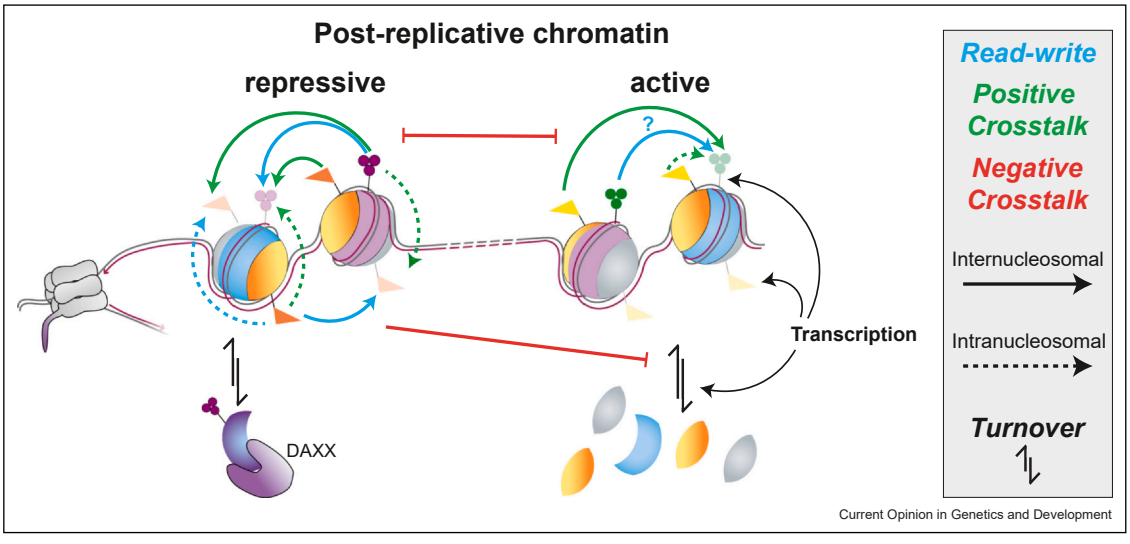
Besides propagating locus-specific epigenetic information by a 'mix'n'match' approach, accurate histone recycling also poses an opportunity to mark genomic regions that are normally devoid of histones in nucleosome-depleted regions (NDRs). These regions show reduced accessibility on nascent chromatin compared with bulk interphase chromatin but get reformed during transcription restart [46,47]. Considering the 'mix'n'-match' model and accurate histone recycling, NDRs would be devoid of parental epigenetic information on all nucleosomal histones but instead harbor naïve, acetylated histones, potentially rendering them prone for eviction (Figure 2d). Supporting this model, parental modifications on both H2A-H2B and H3 are indeed depleted in NDR regions on nascent chromatin [21], while nucleosome occupancy is not [21,46]. It is thus intriguing to think that acetylated nucleosomes are present on NDRs shortly after DNA replication, and this preferential occupancy of new histones facilitates NDR clearing by chromatin remodelers and/or transcription factors. Indeed, both protein classes are enriched on nascent chromatin as revealed by proteomic analysis [48]. In the future, it will be important to determine where these transcriptional regulators bind in nascent chromatin and their impact on restoring NDRs, as they also restore due to transcription restart [47].

Feedback-driven restoration of the epigenome

To mirror the parental chromatin state, naïve histones need to acquire the appropriate locus-specific epigenetic information. This is a major task driven by a wide variety of pathways resulting in modification- and locus-specific restoration kinetics [21,27,49,50]. Here, we focus on mechanisms linked to transmission of information between parental and new histones that operate in an epigenetic fashion. However, the restoration processes as a whole should be viewed as an interplay with DNA sequence (recruitment of transcription factors and chromatin regulators), DNA methylation, noncoding RNAs as well as processes like transcription.

An overarching theme of histone-templated restoration is the use of positive and negative feedback that can work inter- or intra-nucleosomal (Figure 3). Positive feedback takes place using parental histone modifications as template

Figure 3



Histone-templated restoration of parental chromatin states. Nascent chromatin of a repressed and active domains is represented. Old histones are visualized in purple (H3-H4) and gold (H2A-H2B). Parental or *de novo* histone modifications are shown in high or low opacity color, respectively. Arrows depict read–write activities, positive and negative feedback by crosstalk and can take place between nucleosomes (solid lines) or intranucleosomally (dashed lines).

to modify the naïve histones, either by reading and writing the same modification (read–write) or by reading a distinct modification marking the same chromatin state (positive crosstalk). Positive feedback is central for maintenance of repressive histone modifications, such as the Polycomb-mediated deposition of H3K27me3 in facultative heterochromatin or the deposition of H3K9me3 in constitutive heterochromatin.

In facultative heterochromatin, the read–write activity of PRC2 is necessary to maintain H3K27me3 and Polycomb domains (reviewed in Refs. [51,52]), and PRC2 activity is further stimulated by positive crosstalk with H2AK119ub1 and PRC1 (reviewed in Ref. [53]). Similarly, H2AK119ub1 maintenance also depends on the read–write ability of PRC1 [54]. Postreplication, H2AK119ub1 levels are rapidly restored to the pre-replication state, substantially faster than H3K27me3 [21]. H2AK119ub1-reading PRC1 and PRC2 subcomplexes are enriched in postreplicative chromatin [55,56], and restoration of H3K27me3 is delayed in the absence of H2AK119ub1 [21]. This favors a model where H2AK119ub1 recycling fuels its own restoration as well as that of H3K27me3 and Polycomb domains after DNA replication. This also requires rerecruitment of histone H1 [57] that facilitates chromatin compaction and stimulates H3K27me3 and H2A119ub1 spreading [54,58]. Taken together, this indicates that intertwined feedback circuits finetune restoration of Polycomb domains after each round of replication and underscore the role of H3K27me3, as the least dynamic component to be installed last to stabilize the chromatin state and provide memory.

In constitutive heterochromatin, the power of the read–write model of H3K9me2/3 has been clearly demonstrated in fission yeast [59–61]. Moreover, recent analysis of asymmetric histone recycling mutants in mouse embryonic stem cells (mESCs) revealed that maintenance of larger H3K9me3 domains across repeats rely on cis-based inheritance — the basis for read–write — while H3K9me3 in gene regulatory regions do not [5,20]. This illustrates that context matters; propagation mechanisms may carry different weight depending on the local DNA sequence and chromatin makeup. Local density of H3K9me2/3, potentially aided by phase separation of HP1-bound regions, is also a key determinant to whether these domains are propagated epigenetically (reviewed in Ref. [62]). In mammals, we expect crosstalk with DNA methylation, H4K20me3 and macroH2A playing a central role in H3K9me3 restoration post-replication although this remains to be explored. It is also possible that parental histone H3K9me3 templates restoration via a 'read and deposit' mechanism, whereby the H3.3-specific histone chaperone complex DAXX-ATRX is recruited via ATRX binding to H3K9me3 [63] to deposit H3.3 carrying K9me3 in exchange of unmodified new H3.1 [64]. Consistent with this idea, histone turnover at transposable elements involves exchange of canonical H3.1 to the histone variant H3.3 [65], and this is required to maintain H3K9me3 and silencing [66].

Finally, actively transcribed chromatin states are widely decorated with histone modifications, and positive crosstalk has been demonstrated, also between H2A-H2B and H3-H4 (i.e. H2BK120ub1 with H3K4me3/H3K79me3 [67]). Yet how this contributes to post-replication chromatin restoration is unclear. Recent evidence indicates a role for read–write in restoration of H3K4me3 in yeast [31], as mutation of the H3K4me3 reader subunit, Spp1, of the H3K4 methyltransferase complex COMPASS delayed H3K4me3 restoration postreplication. While it is likely that positive feedback operates in active chromatin postreplication, the biological relevance of recycling active modifications remains unclear partly due to rapid restart of transcription [47,68,69], which itself directs the deposition of active chromatin modifications [21]. Recycling of active modifications may act as negative feedback to repel repressive modifications, enabling genes responsive to, for example, environmental input to remain in a competent state for future transcriptional activation (Figure 3).

Using MCM2 and POLE3/4 H3-H4 binding mutants that bias histone recycling asymmetrically to one strand, the significance of faithful cis-based histone inheritance was directly tested in mESCs [5,6,20,70], cancer cells [71], and yeast [18,20,28]. All studies highlighted the vulnerability of repressive domains to skewed histone recycling, such as reduced silencing of repeats in mESCs [5,20] and of the normally repressed mating type region in yeast [18,20,28]. For H3K27me3, bivalent genes decorated with H3K4me3 and H3K27me3 became deregulated [5,6]. Intriguingly, the global levels of H3K27me3 increased due to elevated deposition outside Polycomb domains and H3K9me3 redistributed from repeats to the nonrepetitive genome, indicating that read–write activities focus enzymatic activities to the correct sites and prevent promiscuous deposition at unwanted loci. These loci are normally decorated by H3K36me2/3 or H3K27ac, repelling Polycomb activity [72,73], suggesting that negative feedback from parental histones distributed on both daughter strands contribute to limiting unwarranted modifications and reduce epigenetic noise (Figure 3). In cancer cells, asymmetric histone inheritance promotes tumor growth and facilitates the formation of subclones with increased fitness [71]. This likely reflects that defective recycling enhances heterogeneity and thereby enable new and more aggressive cancer cell fates.

Transforming transient signals to long-term memory

Restoration of nucleosome organization postreplication does not result in a static landscape, but rather in an equilibrium state, where deposition and removal kinetics are at balance. Turnover kinetics vary drastically depending on the chemical modifications, histone variants, and histone type with histone H2A-H2B undergoing substantial replication-independent turnover and histone H3-H4 generally being more stable [65,74,75]. Hence, recycling of parental histones during replication does not necessarily mean that the exact same histones with their parental modifications are inherited across mitosis to daughter cells. This will depend on histone- and modification-specific turnover kinetics, and inheritance of the same modified histone across both replication and mitosis is therefore likely most prevalent for repressive, and relatively stable, H3-H4 methylation [29]. Yet, dynamic modifications and histones, such as H2A-H2B, acetylation, and ubiquitination, can play important roles in regulating *de novo* modification of naïve histones postreplication and hereby contribute to propagation of a chromatin state to daughter cells. Indeed, recycled H2AK119ub1 recruits PRC2 to guide *de novo* H3K27me3 deposition [21], while H3K27ac gets quickly installed on naïve histones if negative feedback from parental H3-H4 is missing [5]. Therefore, early events in nascent chromatin can have a decisive impact on chromatin restoration, with short-term memory components aiding (and potentially rewiring) the establishment of longer-term memory after each round of replication.

Conclusion and perspective

Chromatin replication poses a threat to specialized chromatin states. This renders cells vulnerable to chromatin changes that can challenge silencing of transposable elements and maintenance of cell type–specific transcriptional programs. To reduce such vulnerability, cells have evolved multiple pathways that orchestrate faithful propagation of chromatin states across DNA replication. Dedicated histone chaperones and binding activities integrated into the replication machinery transfer histones with their modifications to both daughter strands in an accurate and symmetric manner. Recycled histones get matched with naïve histones to reduce the risk of forming 'blank' nucleosomes lacking parental epigenetic information. Finally, multilayered feedback within and between nucleosomes reimpose the modification landscape to mirror the parental state. These feedback loops and other restoration mechanisms operate with distinct kinetics for different modifications, resulting in asynchronous oscillation of modifications across the cell cycle. This is likely a source of cellular plasticity, but whether and how it may prime for controlled and uncontrolled cell fate changes during differentiation and disease processes is an open area of research. It may explain how re-entry into the cell cycle in carcinogenesis and processes such as tissue repair can unlock plasticity normally associated with stem cells and thereby drive (unwarranted) cell fate changes. Intriguingly, normal cell state transitions linked to the cell cycle in mESCs are perturbed in histone recycling mutants [5,6], suggesting a connection to chromatin restoration kinetics. Unveiling how dividing cells balance epigenome maintenance versus plasticity necessitates a much more comprehensive understanding of chromatin replication and restoration. We also still lack in-depth understanding of histone recycling mechanisms, especially for H2A-H2B, and of how fork progression and DNA synthesis mechanistically is co-ordinated with histone recycling and nucleosome assembly. Moreover, the impact of replication on 3D genome organization, the mechanisms underlying transcription restart, and the reassociation of chromatin components beyond histone modifications remain sparsely explored and represent important areas of investigation. Finally, a key task is to understand the integration of these multilayered regulatory restoration mechanisms and how the process may be jeopardized in aging and cancer where epigenome fidelity deteriorates.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Zhang W, Qu J, Liu G-H, Belmonte JCI: **The ageing epigenome and its rejuvenation**. *Nat Rev Mol Cell Biol* 2020, **21**:137-150.
2. Reichard J, Zimmer-Bensch G: **The epigenome in neurodevelopmental disorders**. *Front Neurosci* 2021, **15**:776809.
3. Zhao S, Allis CD, Wang GG: **The language of chromatin modification in human cancers**. *Nat Rev Cancer* 2021, **21**:413-430.
4. Fitz-James MH, Cavalli G: **Molecular mechanisms of transgenerational epigenetic inheritance**. *Nat Rev Genet* 2022, **23**:325-341.

5. •• Wenger A, Biran A, Alcaraz N, Redó-Riveiro A, Sell AC, Krautz R, Flury V, Reverón-Gómez N, Solis-Mezarino V, Völker-Albert M, *et al.*: **Symmetric inheritance of parental histones governs epigenome maintenance and embryonic stem cell identity**. *Nat Genet* 2023, **55**:1567-1578.

This study dissects the consequences of asymmetric histone recycling on gene expression and developmental potential in mESCs, defining the importance of cis-based histone inheritance during DNA replication.

6. Wen Q, Zhou J, Tian C, Li X, Song G, Gao Y, Sun Y, Ma C, Yao S, Liang X, *et al.*: **Symmetric inheritance of parental histones contributes to safeguarding the fate of mouse embryonic stem cells during differentiation**. *Nat Genet* 2023, **55**:1555-1566.

7. Gonzalez I, Molliex A, Navarro P: **Mitotic memories of gene activity**. *Curr Opin Cell Biol* 2021, **69**:41-47.

8. Petryk N, Bultmann S, Bartke T, Defossez P-A: **Staying true to yourself: mechanisms of DNA methylation maintenance in mammals**. *Nucleic Acids Res* 2021, **49**:3020-3032.

9. Bandau S, Alvarez V, Jiang H, Graff S, Sundaramoorthy R, Gierlinski M, Toman M, Owen-Hughes T, Sidoli S, Lamond A, Alabert C: **RNA polymerase II promotes the organization of chromatin following DNA replication**. *EMBO Rep* 2024,.

10. Bruno F, Coronel-Guisado C, González-Aguilera C: **Collisions of RNA polymerases behind the replication fork promote alternative RNA splicing in newly replicated chromatin**. *Mol Cell* 2024, **84**:221-233.

11. Groth A, Roche D, Corpet A, Almouzni G, Lukas J, Bartek J, Cook AJL: **Regulation of replication fork progression through histone supply and demand**. *Science* 2007, **318**:1928-1931.

12. Foltman M, Evrin C, De Piccoli G, Jones RC, Edmondson RD, Katou Y, Nakato R, Shirahige K, Labib K: **Eukaryotic replisome components cooperate to process histones during chromosome replication**. *Cell Rep* 2013, **3**:892-904.

13. Huang H, Strømme CB, Saredi G, Hödl M, Strandsby A, González-Aguilera C, Chen S, Groth A, Patel DJ: **A unique binding mode enables MCM2 to chaperone histones H3-H4 at replication forks**. *Nat Struct Mol Biol* 2015, **22**:618-626.

14. Petryk N, Dalby M, Wenger A, Stromme CB, Strandsby A, Andersson R, Groth A: **MCM2 promotes symmetric inheritance of modified histones during DNA replication**. *Science* 2018, **361**:1389-1392.

15. Gan H, Serra-Cardona A, Hua X, Zhou H, Labib K, Yu C, Zhang Z: **The Mcm2-Ctf4-Polα axis facilitates parental histone H3-H4 transfer to lagging strands**. *Mol Cell* 2018, **72**:140-151.e3.

16. Zasadzinska E, Huang J, Bailey AO, Guo LY, Lee NS, Srivastava S, Wong KA, French BT, Black BE, Foltz DR: **Inheritance of CENP-A Nucleosomes during DNA Replication Requires HJURP**. *Dev Cell* 2018, **47**:348-362.

17. Bellelli R, Belan O, Pye VE, Clement C, Maslen SL, Skehel JM, Cherepanov P, Almouzni G, Boulton SJ: **POLE3-POLE4 is a histone H3-H4 chaperone that maintains chromatin integrity during DNA replication**. *Mol Cell* 2018, **72**:112-126.e5.

18. Yu C, Gan H, Serra-Cardona A, Zhang L, Gan S, Sharma S, Johansson E, Chabes A, Xu R, Zhang Z: **A mechanism for preventing asymmetric histone segregation onto replicating DNA strands**. *Science* 2018, **8849**:eaat8849.

19. Evrin C, Maman JD, Diamante A, Pellegrini L, Labib K: **Histone H2A-H2B binding by Pol α in the eukaryotic replisome contributes to the maintenance of repressive chromatin**. *EMBO J* 2018, **37**:e99021.

20. Li Z, Hua X, Serra-Cardona A, Xu X, Gan S, Zhou H, Yang W-S, Chen C, Xu R-M, Zhang Z: **DNA polymerase α interacts with H3-H4 and facilitates the transfer of parental histones to lagging strands**. *Sci Adv* 2020, **6**:eabb5820.

21. •• Flury V, Reverón-Gómez N, Alcaraz N, Stewart-Morgan KR, Wenger A, Klose RJ, Groth A: **Recycling of modified H2A-H2B provides short-term memory of chromatin states**. *Cell* 2023, **186**:1050-1065.e19.

This study identifies accurate parental H2A-H2B recycling in a manner independent from H3-H4 recycling and postulates intra- and inter-nucleosomal crosstalk for chromatin restoration in mESCs.

22. Hammond CM, Strømme CB, Huang H, Patel DJ, Groth A: **Histone chaperone networks shaping chromatin function**. *Nat Rev Mol Cell Biol* 2017, **18**:141-158.

23. Safaric B, Chacin E, Scherr MJ, Rajappa L, Gebhardt C, Kurat CF, Cordes T, Duderstadt KE: **The fork protection complex recruits FACT to reorganize nucleosomes during replication**. *Nucleic Acids Res* 2022, **50**:1317-1334.

24. • Wang X, Tang Y, Xu J, Leng H, Shi G, Hu Z, Wu J, Xiu Y, Feng J, Li Q: **The N-terminus of Spt16 anchors FACT to MCM2–7 for parental histone recycling**. *Nucleic Acids Res* 2023, **51**:11549-11567.

This article identifies FACT in co-ordinating histone recycling with MCM2 by direct and histone-mediated interactions with the replisome in yeast.

25. Wang P, Yang W, Zhao S, Nashun B: **Regulation of chromatin structure and function: insights into the histone chaperone FACT**. *Cell Cycle* 2021, **20**:465-479.

26. •• Ehara H, Kujirai T, Shirouzu M, Kurumizaka H, Sekine S: **Structural basis of nucleosome disassembly and reassembly by RNAPII elongation complex with FACT**. *Science* 2022, **377**:eabp9466.

Using cryoelectron microscopy, this study highlights the role of FACT in histone recycling during RNAPII-mediated transcription through a nucleosome, emphasizing the role of FACT in maintaining a hexasome and tethered H2A-H2B dimer.

27. Reverón-Gómez N, González-Aguilera C, Stewart-Morgan KR, Petryk N, Flury V, Graziano S, Johansen JV, Jakobsen JS, Alabert C, Groth A: **Accurate recycling of parental histones reproduces the histone modification landscape during DNA replication**. *Mol Cell* 2018, **72**:239-249.e5.

28. Schlissel G, Rine J: **The nucleosome core particle remembers its position through DNA replication and RNA transcription**. *Proc Natl Acad Sci* 2019, **116**:201911943.

29. Escobar TM, Oksuz O, Saldaña-Meyer R, Descostes N, Bonasio R, Reinberg D: **Active and repressed chromatin domains exhibit distinct nucleosome segregation during DNA replication**. *Cell* 2019, **179**:953-963.e11.

30. Wooten M, Snedeker J, Nizami ZF, Yang X, Ranjan R, Urban E, Kim JM, Gall J, Xiao J, Chen X: **Asymmetric histone inheritance via strand-specific incorporation and biased replication fork movement**. *Nat Struct Mol Biol* 2019, **26**:732-743.

31. •• Serra-Cardona A, Duan S, Yu C, Zhang Z: **H3K4me3 recognition by the COMPASS complex facilitates the restoration of this histone mark following DNA replication**. *Sci Adv* 2022, **8**:eabm6246.

This article identifies a read–write role of H3K4me3 and COMPASS in restoring the active chromatin landscape in yeast, identifying a role of read–write activity in active chromatin.

32. Shan Z, Zhang Y, Bu J, Li H, Zhang Z, Xiong J, Zhu B: **The patterns and participants of parental histone recycling during DNA replication in Saccharomyces cerevisiae**. *Sci China Life Sci* 2023, **66**:1600-1614.

33. Xu X, Duan S, Hua X, Li Z, He R, Zhang Z: **Stable inheritance of H3.3-containing nucleosomes during mitotic cell divisions**. *Nat Commun* 2022, **13**:2514.

34. • Mühlen D, Li X, Dovgusha O, Jäckle H, Günesdogan U: **Recycling of parental histones preserves the epigenetic landscape during embryonic development**. *Sci Adv* 2023, **9**:eadd6440.

Using an elegant *in vivo* system in Drosophila lacking *de novo* histone supply, this work demonstrates accurate redeposition of parental H2A/H2B/H3/H4 after DNA replication in living embryos.

35. Zion E, Chen X: **Studying histone inheritance in different systems using imaging-based methods and perspectives**. *Biochem Soc Trans* 2023, **51**:1035-1046.

36. Annunziato A: **The fork in the road: histone partitioning during DNA replication**. *Genes* 2015, **6**:353-371.

37. Jiang D, Berger F: **DNA replication-coupled histone modification maitains Polycomb gene silencing in plants**. *Science* 2017, **4965**:1146-1149.

38. Yang H, Berry S, Olsson TSG, Hartley M, Howard M, Dean C: **Distinct phases of Polycomb silencing to hold epigenetic memory of cold in *Arabidopsis***. *Science* 2017, **357**:1142-1145.

39. Saxton DS, Rine J: **Epigenetic memory independent of symmetric histone inheritance**. *eLife* 2019, **8**:760801.

40. Nickels JF, Edwards AK, Charlton SJ, Mortensen AM, Hougaard SCL, Trusina A, Sneppen K, Thon G: **Establishment of heterochromatin in domain-size-dependent bursts**. *Proc Natl Acad Sci* 2021, **118**:e2022887118.

41. Nekrasov M, Amrichova J, Parker BJ, Soboleva TA, Jack C, Williams R, Huttley GA, Tremethick DJ: **Histone H2A.Z inheritance during the cell cycle and its impact on promoter organization and dynamics**. *Nat Struct Mol Biol* 2012, **19**:1076-1083.

42. Murphy PJ, Wu SF, James CR, Wike CL, Cairns BR: **Placeholder nucleosomes underlie germline-to-embryo DNA methylation reprogramming**. *Cell* 2018, **172**:993-1006.e13.

43. Ibarra-Morales D, Rauer M, Quarato P, Rabbani L, Zenk F, Schulte-Sasse M, Cardamone F, Gomez-Auli A, Cecere G, Iovino N: **Histone variant H2A.Z regulates zygotic genome activation**. *Nat Commun* 2021, **12**:7002.

44. Liu X, Zhang J, Zhou J, Bu G, Zhu W, He H, Sun Q, Yu Z, Xiong W, Wang L, *et al.*: **Hierarchical accumulation of histone variant H2A.Z regulates transcriptional states and histone modifications in early mammalian embryos**. *Adv Sci* 2022, **9**:2200057.

45. Oberdoerffer P, Miller KM: **Histone H2A variants: diversifying chromatin to ensure genome integrity**. *Semin Cell Dev Biol* 2023, **135**:59-72.

46. Ramachandran S, Henikoff S: **Transcriptional regulators compete with nucleosomes post-replication**. *Cell* 2016, **165**:580-592.

47. Stewart-Morgan KR, Reverón-Gómez N, Groth A: **Transcription restart establishes chromatin accessibility after DNA replication**. *Mol Cell* 2019, **75**:284-297.e6.

48. Alvarez V, Bandau S, Jiang H, Rios-Szwed D, Hukelmann J, Garcia-Wilson E, Wiechens N, Griesser E, Ten Have S, Owen-Hughes T, *et al.*: **Proteomic profiling reveals distinct phases to the restoration of chromatin following DNA replication**. *Cell Rep* 2023, **42**:111996.

49. Alabert C, Barth TK, Reverón-Gómez N, Sidoli S, Schmidt A, Jensen ON, Imhof A, Groth A: **Two distinct modes for propagation of histone PTMs across the cell cycle**. *Genes Dev* 2015, **29**:585-590.

50. Van Rechem C, Ji F, Chakraborty D, Black JC, Sadreyev RI, Whetstine JR: **Collective regulation of chromatin modifications predicts replication timing during cell cycle**. *Cell Rep* 2021, **37**:109799.

51. Reinberg D, Vales LD: **Chromatin domains rich in inheritance**. *Science* 2018, **361**:33-34.

52. Laugesen A, Højfeldt JW, Helin K: **Molecular mechanisms directing PRC2 recruitment and H3K27 methylation**. *Mol Cell* 2019, **74**:8-18.

53. Blackledge NP, Klose RJ: **The molecular principles of gene regulation by Polycomb repressive complexes**. *Nat Rev Mol Cell Biol* 2021, **22**:815-833.

54. Zhao J, Wang M, Chang L, Yu J, Song A, Liu C, Huang W, Zhang T, Wu X, Shen X, *et al.*: **RYBP/YAF2-PRC1 complexes and histone H1-dependent chromatin compaction mediate propagation of H2AK119ub1 during cell division**. *Nat Cell Biol* 2020, **22**:439-452.

55. • Asenjo HG, Gallardo A, López-Onieva L, Tejada I, Martorell-Marugán J, Carmona-Sáez P, Landeira D: **Polycomb regulation is coupled to cell cycle transition in pluripotent stem cells**. *Sci Adv* 2020, **6**:eaay4768.

This article dissects the recruitment of PRC2 subcomplexes across distinct cell cycle phases and their role in differentiation decision in mESCs, highlighting the prevalent role of H2AK119ub1 of recruiting reader complexes in G2.

56. Takano J, Ito S, Dong Y, Sharif J, Nakajima-Takagi Y, Umeyama T, Han Y-W, Isono K, Kondo T, Iizuka Y, *et al.*: **PCGF1-PRC1 links chromatin repression with DNA replication during hematopoietic cell lineage commitment**. *Nat Commun* 2022, **13**:7159.

57. Liu C, Yu J, Song A, Wang M, Hu J, Chen P, Zhao J, Li G: **Histone H1 facilitates restoration of H3K27me3 during DNA replication by chromatin compaction**. *Nat Commun* 2023, **14**:4081.

58. Willcockson MA, Healton SE, Weiss CN, Bartholdy BA, Botbol Y, Mishra LN, Sidhwani DS, Wilson TJ, Pinto HB, Maron MI, *et al.*: **H1 histones control the epigenetic landscape by local chromatin compaction**. *Nature* 2021, **589**:293-298.

59. Zhang K, Mosch K, Fischle W, Grewal SIS: **Roles of the Clr4 methyltransferase complex in nucleation, spreading and maintenance of heterochromatin**. *Nat Struct Mol Biol* 2008, **15**:381-388.

60. Ragunathan K, Jih G, Moazed D: **Epigenetic inheritance uncoupled from sequence-specific recruitment**. *Science* 2015, **348**:1258699.

61. Allshire RC, Madhani HD: **Ten principles of heterochromatin formation and function**. *Nat Rev Mol Cell Biol* 2018, **19**:229-244.

62. Grewal SIS: **The molecular basis of heterochromatin assembly and epigenetic inheritance**. *Mol Cell* 2023, **83**:1767-1785.

63. Eustermann S, Yang J-C, Law MJ, Amos R, Chapman LM, Jelinska C, Garrick D, Clynes D, Gibbons RJ, Rhodes D, *et al.*: **Combinatorial readout of histone H3 modifications specifies localization of ATRX to heterochromatin**. *Nat Struct Mol Biol* 2011, **18**:777-782.

64. Carraro M, Hendriks IA, Hammond CM, Solis-Mezarino V, Völker-Albert M, Elsborg JD, Weisser MB, Spanos C, Montoya G, Rappsilber J, *et al.*: **DAXX adds a de novo H3.3K9me3 deposition pathway to the histone chaperone network**. *Mol Cell* 2023, **83**:1075-1092.e9.

65. Dunjić M, Jonas F, Yaakov G, More R, Mayshar Y, Rais Y, Orenbuch A-H, Cheng S, Barkai N, Stelzer Y: **Histone exchange sensors reveal variant specific dynamics in mouse embryonic stem cells**. *Nat Commun* 2023, **14**:3791.

66. Elsässer SJ, Noh K-M, Diaz N, Allis CD, Banaszynski LA: **Histone H3.3 is required for endogenous retroviral element silencing in embryonic stem cells**. *Nature* 2015, **522**:240-244.

67. Fields JK, Hicks CW, Wolberger C: **Diverse modes of regulating methyltransferase activity by histone ubiquitination**. *Curr Opin Struct Biol* 2023, **82**:102649.

68. Tsirkas I, Dovrat D, Thangaraj M, Brouwer I, Cohen A, Paleiov Z, Meijler MM, Lenstra T, Aharoni A: **Transcription-replication coordination revealed in single live cells**. *Nucleic Acids Res* 2022, **50**:2143-2156.

69. Fenstermaker TK, Petruk S, Kovermann SK, Brock HW, Mazo A: **RNA polymerase II associates with active genes during DNA replication**. *Nature* 2023, **620**:426-433.

70. Xu X, Hua X, Brown K, Ren X, Zhang Z: **Mcm2 promotes stem cell differentiation via its ability to bind H3-H4**. *eLife* 2022, **11**:e80917.

71. • Tian C, Zhou J, Li X, Gao Y, Wen Q, Kang X, Wang N, Yao Y, Jiang J, Song G, *et al.*: **Impaired histone inheritance promotes tumor progression**. *Nat Commun* 2023, **14**:3429.

This study reveals the consequences of asymmetric histone recycling on gene expression and tumor evolution in MCF-7 cancer cells, highlighting the importance of cis-based histone inheritance during DNA replication.

72. Schmitges FW, Prusty AB, Faty M, Stützer A, Lingaraju GM, Aiwazian J, Sack R, Hess D, Li L, Zhou S, *et al.*: **Histone methylation by PRC2 is inhibited by active chromatin marks**. *Mol Cell* 2011, **42**:330-341.

73. Streubel G, Watson A, Jammula SG, Scelfo A, Fitzpatrick DJ, Oliviero G, McCole R, Conway E, Glancy E, Negri GL, *et al*.: **The H3K36me2 methyltransferase Nsd1 demarcates PRC2-mediated H3K27me2 and H3K27me3 domains in embryonic stem cells**. *Mol Cell* 2018, **70**:371-379.e5.

74. • Yaakov G, Jonas F, Barkai N: **Measurement of histone replacement dynamics with genetically encoded exchange timers in yeast**. *Nat Biotechnol* 2021, **39**:1434-1443.

This article introduces the 'histone exchange timer', a powerful technology to measure histone deposition, eviction, and exchange genome-wide with locus-specific information.

75. Kimura H, Cook PR: **Kinetics of core histones in living human cells: little exchange of H_3 and H_4 and some rapid exchange of H_2B**. *J Cell Biol* (7) 2001, **153**:1341-1353.