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The roles of symmetric and asymmetric parental histone recycling in cell fate, development, and disease

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Replication of the epigenome occurs concurrently with DNA replication. A major component of epigenetic memory is contained in histones, and this memory is preserved via recycling of parental histones onto the leading and lagging strands of the replication fork. The histones of one parental strand must be incorporated into two nascent strands, a process governed by the replisome's histone chaperones. These chaperones determine which strand each histone is incorporated into and the frequency with which each strand receives parental histones, a determination that is essential for preserving epigenetic landscapes and ensuring proper gene expression following DNA replication. Here, we describe recent developments in our understanding of how parental histone recycling occurs and the effects it has on cells in developmental contexts. Although histones are generally recycled symmetrically to the leading and lagging strands, asymmetric histone recycling can occur naturally in some asymmetrically dividing cells or be induced by manipulating replisome components. Asymmetric histone recycling generates distinct epigenetic states at a given genomic locus, which can result in differential gene expression and ultimately different cell fates following cell division in multicellular organisms. This is important for future studies examining the role of epigenetics in both development and disease contexts.

1. Introduction

DNA replication is an essential and defining aspect of life. This fundamental process has been studied since the 1950s, when the semi-conservative nature of DNA replication was suggested to be an inherent property of its base pairing structure [1–5]. Later, the functional roles of the epigenome, the non-genomic regulatory elements of the nucleus, began to be explored [6]. During the second half of the twentieth century, DNA methylation was proposed to regulate gene activity (reviewed in [7,8]), and histone modifications were linked to RNA synthesis before being recognized for their own regulatory roles [9,10]. These epigenetic modifications to either histones or DNA work in coordination to regulate the accessibility of specific DNA regions, and this can vary with respect to different tissues, environmental stressors and age (reviewed in [11,12]). In eukaryotic cells, DNA replication occurs concurrently with epigenome duplication and re-establishment, processes that preserve or remodel epigenetic information on the two newly replicated DNA molecules. Because epigenetic information provides information for organizing chromatin and regulating gene expression, proper epigenetic inheritance is essential for normal cellular function and organismal survival.

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The coordinated replication of the genome and epigenome is a highly complex process. In this review, we focus on recent advances in one fundamental aspect of epigenome replication: the recycling of pre-existing histones at the replication fork.

Histones are the proteins around which DNA is wrapped to form nucleosomes, each of which contains a core octamer composed of two H2A–H2B dimers and one $(H3–H4)_2$ tetramer. Post-translational modifications of histones play major roles in recruiting transcription factors and chromatin-modifying enzymes that regulate gene expression. For example, trimethylation of H3 lysine 9 (H3K9me3) is associated with constitutive heterochromatin and gene silencing, whereas trimethylation of H3 lysine 4 (H3K4me3) is associated with active transcription, particularly at promoter regions (reviewed in [13]). Together with nucleosome density and histone variants, these modifications influence chromatin accessibility and the expression of nearby genes.

Unlike DNA methylation, histone modifications reside on histone proteins rather than on the DNA itself. While DNA methylation remains stably associated with DNA until it is enzymatically removed or passively diluted during replication, histone modifications are more dynamic. For example, they can be rewritten or erased by different histone-modifying enzymes, or they can be changed through the incorporation of new histones. This flexibility enables epigenetic regulation to dynamically respond to environmental changes and developmental cues (reviewed in [14]).

During DNA replication, as the amount of DNA doubles, so too must the number of incorporated histones increase. 'New histones' refer to those incorporated during or after recent replication, whereas 'parental' (or 'old') histones are those already incorporated in the parental DNA prior to S phase. Recycling of parental histones onto nascent DNA is essential for propagating epigenetic information and preserving local chromatin states [15–17]. Accordingly, parental histone recycling is a key regulator of both stable gene expression and developmental plasticity in multicellular organisms. Under most studied circumstances, histones are symmetrically partitioned between sister chromatids to maintain epigenetic memory. Disruption of this process can instead bias histone transfer towards one chromatid, generating epigenetic asymmetry. In some developmental contexts, such asymmetry is not aberrant but rather functional, serving as a potential mechanism to differentially prime daughter cells for distinct cell fates through global or locus-specific epigenetic differences, as discussed later in this review.

Recent advances have shed light on the proteins and mechanisms regulating symmetric and asymmetric histone recycling, along with improved techniques and tools for analysing histones and their modifications behind a replication fork. At the most fundamental level, DNA replication is initiated by origin firing and progression of the replication fork, spearheaded by the Cdc45-Mcm-GINS (CMG) helicase complex. The Mcm2-7 helicase unwinds parental DNA, separating the two strands for semi-conservative replication. One strand serves as the template for continuous leading-strand synthesis by DNA polymerase ε (polε), whereas the lagging strand is synthesized discontinuously as Okazaki fragments through the coordination of primase, DNA polymerase α (polα), DNA polymerase δ (polδ) and DNA ligase I (reviewed in [18]). Together, these processes produce two identical daughter DNA strands via distinct leading- and lagging-strand synthesis mechanisms.

As the replication fork progresses, the CMG complex encounters nucleosomes containing parental histones that contribute to the pre-existing epigenomic landscape [19,20]. Hence, a central challenge faced by the passing replication fork is the reliable recycling of these parental histones to the same location onto nascent DNA to restore chromatin states after replication. Under canonical conditions, sufficient parental histones must be recycled to both daughter strands to re-establish symmetric epigenomes (figure 1A). New histones are then modified by histone-modifying enzymes through 'read–write' mechanisms that propagate modifications from local parental histones [21]. By contrast, when asymmetric histone incorporation is required to modify the epigenetic landscape, replisome dynamics can be modified to bias parental histone incorporation towards one daughter strand, with the opposite strand preferentially enriched with new histones (figure 1B,C).

Among the four core histones, the $(H3–H4)_2$ tetramer and its modifications are more likely to be stably maintained during DNA replication, whereas the H2A–H2B dimers can be more readily exchanged during nucleosome disassembly and reassembly [22] (reviewed in [23]). However, recent work suggests that H2A–H2B dimers and their modifications can also be recycled independently of $(H3–H4)_2$, contributing to the rapid restoration of chromatin states following DNA replication [22]. Similar recycling mechanisms also apply to histone variants. For example, the H3 variant H3.3, which is typically incorporated independently of DNA replication at active genes, can likely be recycled during replication in a manner similar to canonical H3 [24,25].

This review highlights recent advances in the mechanisms of parental histone recycling at the replication fork. We first discuss how parental histones are symmetrically recycled to preserve epigenetic information and then discuss how these processes can be modified to generate asymmetric histone patterns between sister chromatids during multicellular development and pathogenesis. Because DNA replication and epigenetic inheritance are fundamentally linked to broader organism health, understanding replication-coupled histone recycling should provide new insights into the regulation of cell fate, growth and development, and the origins of cancer, ageing and developmental disorders.

2. Symmetric histone recycling

When a cell propagates similar epigenomes, it must effectively maintain equivalent chromatin environments on both daughter strands during DNA replication. One mechanism that helps achieve this symmetry is the comparable recycling of parental histones onto the leading and lagging strands. Because H2A–H2B dimers can be dynamically exchanged from the nucleosome core [22] (reviewed in [23]), recycling of the parental $(H3–H4)_2$ tetramer is thought to be the primary contributor to daughter-strand symmetry. Subsequently, new histones are incorporated onto both strands to fill the remaining gaps. Although incorporation of new histones dilutes the abundance of mature, post-translationally modified $(H3–H4)_2$ by up to 50%, reader–writer enzymes can propagate many histone modifications by copying them from recycled parental histones onto newly incorporated histones, thus

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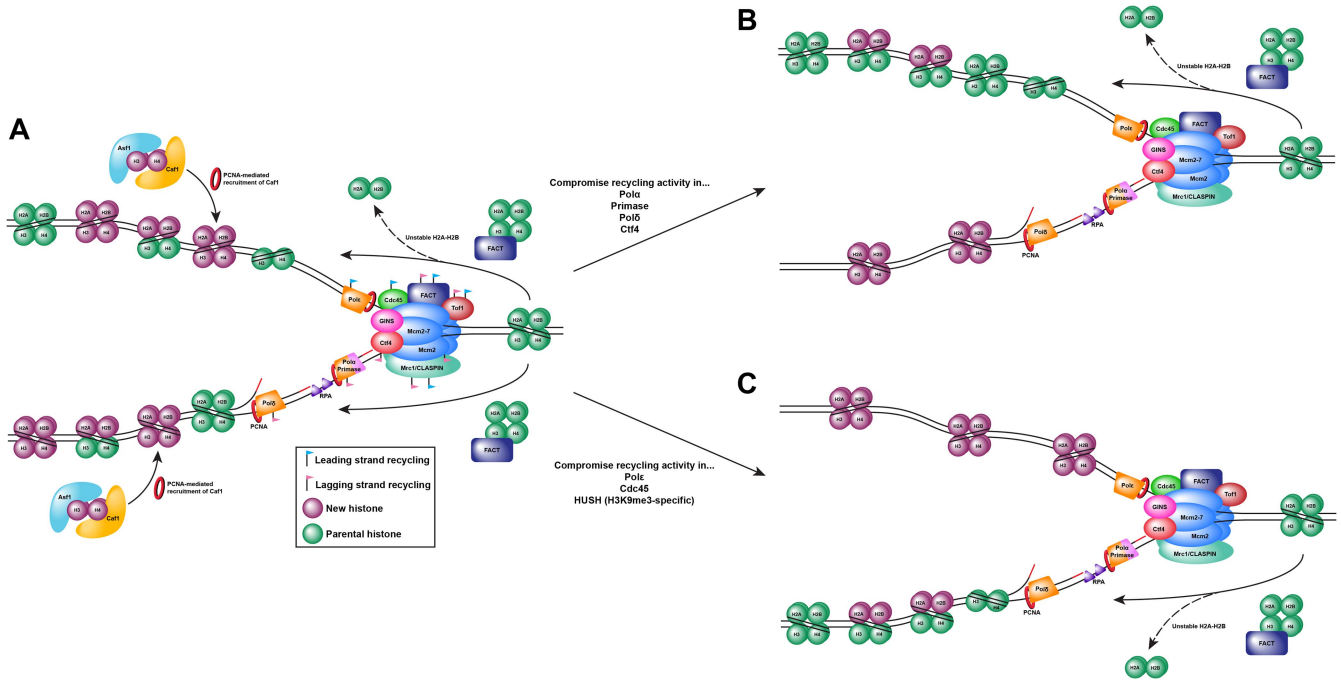


Figure 1. Replication-coupled histone recycling. (A) Replisome components bind parental histones as they are encountered and transfer them to either the leading or lagging strand through distinct mechanisms. (B,C) Compromising the histone chaperoning ability of the proteins involved in strand-specific recycling can result in biased recycling to one strand and low density, new histone incorporation on the other strand.

preserving chromatin structure [21]. Nevertheless, different histone modifications are restored with distinct kinetics following replication [26].

The mechanisms regulating the symmetric recycling of parental histones onto the leading and lagging strands have been extensively reviewed (e.g. [27–29]). Here, we briefly summarize key advances, focusing on discoveries from the past decade. Many of these have been enabled by technological innovations, such as the methods listed in table 1. In particular, enrichment and sequencing of protein-associated nascent DNA (eSPAN) and sister chromatids after replication sequencing (SCAR-seq) have revolutionized our ability to measure histone incorporation at replication forks in a locus- and strand-specific manner [34,37]. Additional strand-specific sequencing methods have been developed to capture diverse aspects of replication dynamics, providing unprecedented insights into the interplay between the replisome, histones, DNA modifications, DNA damage and replication fork blocks (reviewed in [30]).

2.1. Capture of parental histones

As the replication fork progresses, the opening helicase encounters a nucleosome approximately every 150–200 base pairs (reviewed in [38]). The protein complex facilitates chromatin transactions (FACT) binds to and destabilizes nucleosomes as the fork progresses [39]. In budding yeast, this process is promoted by interactions involving the N-terminus of Spt16—a FACT subunit—and Tof1 [40,41]. Furthermore, the histone chaperone Asf1 binds to parental histones as their interactions with DNA are disrupted, facilitating their subsequent recycling during replication-coupled nucleosome assembly [42,43].

Mcm2 also contributes to parental histone recycling through its intrinsically disordered N-terminal tail that binds the $(H3–H4)_2$ tetramer [43,44]. Structural studies suggest that Mcm2, Asf1 and $(H3–H4)_2$ form a transient complex that can act as a histone transfer intermediate, enabling deposition of parental histones behind the helicase or hand-off to other histone chaperones [45]. Following capture by FACT, Asf1, Mcm2 and other replisome factors, parental histones are primed for recycling onto either the leading or lagging strand through the distinct recycling pathways described below.

2.2. Leading-strand recycling

The polε accessory subunits POLE3 and POLE4 (Dpb3 and Dpb4 in yeast) form a histone-binding dimer that promotes parental $(H3–H4)_2$ transfer to the leading strand during DNA replication in both yeast and mammalian cells [46,47]. Polε is coupled to the CMG complex via its interaction with Psf1, a component of the GINS (Sld5, Psf1, Psf2, Psf3) complex, thereby tethering polε to the replisome and coordinating leading-strand synthesis with fork progression [48]. This association places the POLE3–POLE4 histone chaperone in a proper position to recycle parental histones onto the leading strand. By contrast, lagging-strand synthesis is inherently discontinuous and relies on polymerases that dynamically dissociate from and reassociate with the replisome during Okazaki fragment synthesis [49].

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Table 1. Techniques for assessing histone and chromatin dynamics. All these methods can target histones and histone modifications. Additional methods reviewed in [30].

method	brief description	advantages	disadvantages
CUT&RUN CUT&TAG	antibody-directed MNase (RUN) or Tn5 (TAG) to target protein, which excise DNA fragments where that protein is bound [31,32]	• genome-wide profile of protein binding • high signal-to-noise	• not specific to replication state • no strand information
eSPAN	BrdU labels nascent DNA, followed by ChIP. At known origin of replication, infer leading versus lagging strand based on direction of replication away from origin [33]	• leading versus lagging strand-specific • profiles entire replication bubble around an origin of replication	• only measures occupancy in close proximity to known origins • requires cell synchronization
SCAR-seq	EdU labels nascent DNA, followed by ChIP. Leading versus lagging strand is determined by OK-seq [34,35]	• leading versus lagging strand-specific • can profile genome-wide, with some limitations	• most effective in regions consistently replicated in the same direction • requires OK-seq data • requires large number of cells
chromatin fibres	EdU labels nascent DNA. Lyse cells to release chromatin, followed by IF and high-resolution microscopy. Infer leading versus lagging strand by labelling a lagging strand-enriched protein such as PCNA [36]	• direct comparison of leading versus lagging strand at individual replication forks • compatible with low cell number • single molecule, reveals fork heterogeneity	• no sequence information • low throughput, a relatively small subset of the genome is sampled • variable stretching of fibres means length cannot be determined

Intriguingly, several model organisms, including *Drosophila melanogaster* and *Caenorhabditis elegans*, lack clear homologues of POLE3 and POLE4. This suggests that other replisome-associated components may play a larger role in leading-strand histone recycling in these species. One possibility is Claspin (discussed below), which could compensate for the absence of POLE3/4.

2.3. Lagging-strand recycling

A series of replisome components facilitates parental histone transfer to the lagging strand. For example, Mcm2, Ctf4 and polα form a histone-binding axis, and each factor is individually required for efficient lagging-strand recycling [15,16,37]. Consistently, mutations that disrupt the histone-binding domains of these components impair lagging-strand histone recycling [16]. Likewise, reducing Okazaki fragment initiation by reducing levels or compromising the activity of the primase-polα complex is sufficient to bias parental histone recycling towards the leading strand [50].

The polδ subunit Pol32 also possesses histone chaperone activity and was recently demonstrated to receive parental histones handed off from Mcm2 for deposition onto the lagging strand [51]. In addition to its canonical role on the lagging strand, emerging evidence indicates that polδ also participates in leading strand synthesis under certain conditions [52–54]. This raises the possibility that polδ could serve as a histone chaperone on either daughter strand, depending on where polδ is engaged during DNA replication. By contrast, the contribution of the primase-polα complex to leading strand synthesis is largely restricted to origin firing and repriming at stalled forks under certain DNA damage conditions [55] (reviewed in [56]).

2.4. Determination of leading- versus lagging-strand recycling

Claspin (Mrc1 in yeast) is a replisome factor that stabilizes replication forks and participates in checkpoint activation [57–59]. Recent studies have demonstrated that Claspin binds the $(H3–H4)_2$ tetramer and promotes parental histone recycling to both the leading and lagging strands [20,60]. Hence, Claspin has been proposed to act as a toggle between leading and lagging strand recycling. However, it remains unclear whether Claspin alternates histone recycling between the leading and lagging strands in a consistent pattern. Likewise, it is unclear whether Claspin can repeatedly recycle parental histones to the same daughter strand when histone transfer to the opposite strand is temporarily impeded. Addressing these questions will be crucial for understanding how the replisome determines the strand-specific inheritance of parental histones.

As increasingly complete replisome structures are computationally reconstructed through molecular dynamics simulations, additional candidate regulators of strand-specific histone recycling have emerged. For example, *in silico* simulations suggest that Cdc45 binding to a parental $(H3–H4)_2$ tetramer directs its transfer to the leading strand, whereas the absence of Cdc45 favours recycling to the lagging strand [44]. Similar simulations suggest that replication protein A (RPA) binding to the lagging strand inhibits parental histone recycling [44]. This prediction aligns with experimental observations that compromised lagging-strand

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synthesis reduces lagging-strand histone recycling, likely because RPA competes with the primase-polα complex for binding to exposed single-stranded DNA [56].

2.5. Defects in symmetric histone recycling

In eukaryotic cells maintaining the same identity over time, proper parental histone recycling during DNA replication is critical for preserving epigenetic information across cell divisions. Mutations in several replication components selectively impair parental histone recycling while maintaining sufficient DNA replication activity to support cell viability, providing powerful genetic tools for investigating the consequences of defective histone inheritance [61]. Disruption of parental histone recycling can result in distinct epigenetic landscapes on the two daughter strands and, consequently, in the two daughter cells following mitosis [20,62,63]. Beyond these immediate changes in chromatin state, defective symmetric histone recycling can trigger downstream effects that influence cell identity and organismal fitness.

In cultured mammalian cells, Mcm2 histone-binding mutants display genome-wide parental histone recycling biased towards the leading strand, resulting in loss of H3K9me3, dysregulation of H3K27me3 and defects in neural differentiation [15,62]. Similarly, disruption of POLE4 activity impairs leading-strand parental histone recycling and causes preferential incorporation of parental histones into the lagging strand [46,47,64]. These defects result in increased H3K27me3 and aberrant gene expression in mouse embryonic stem cells (mESCs), leading to decreased cellular plasticity and defective differentiation [64,65]. Together, these findings demonstrate that faithful parental histone recycling is required to maintain chromatin states that support mESC identity while allowing for proper lineage-specific differentiation.

Defective histone recycling also has consequences beyond epigenetic regulation and gene expression. In budding yeast, the recycling-deficient mutant $mcm2^{3A}$ induces lagging strand-biased parental histone recycling genome-wide, whereas the knockout $dpb3^{\Delta}$ biases recycling towards the leading strand [16,46]. Despite producing opposite strand biases, both mutants, as well as the $mcm2^{3A}$ $dpb3^{\Delta}$ double mutant, exhibit reduced homologous recombination. These findings indicate that proper parental histone recycling is important for maintaining chromatin structures that support efficient DNA repair and genome integrity [66]. One possible explanation is that defective histone recycling increases the pool of free histones, thereby perturbing chromatin assembly and homologous recombination.

Together, these findings demonstrate that parental histone recycling coordinates epigenetic inheritance with genome maintenance and cell fate. By preserving chromatin organization during DNA replication, faithful histone recycling enables stable cell identity while maintaining the genome integrity required for normal development and cellular function.

3. Asymmetric parental histone recycling in multicellular organisms

While faithful symmetric histone recycling preserves epigenetic information, developmental contexts could require breaking epigenetic symmetry to generate distinct cell fates in multicellular organisms. In some cases, such asymmetry may not only be beneficial but necessary. Altering parental histone recycling could permit selective reconfiguration of chromatin states, allowing certain epigenetic information to be reset while others are retained. This principle is especially relevant in asymmetrically dividing cells, where differential inheritance of parental histones may facilitate the establishment of distinct chromatin landscapes in the two daughter cells. In principle, reduced inheritance of parental histones on one sister chromatid could facilitate the establishment of a new epigenetic landscape and corresponding gene expression programme, whereas faithful parental histone inheritance on the other sister chromatid could help preserve the original cell state. Notably, asymmetric cell division does not necessarily require asymmetric histone recycling, as many intrinsic and extrinsic mechanisms contribute to daughter cell asymmetry. Rather, asymmetric parental histone inheritance should be viewed as one mechanism for promoting epigenetic remodelling and cell fate divergence in specific developmental or regenerative contexts, as discussed below.

3.1. Histone asymmetry in *Drosophila*

Asymmetric parental histone inheritance is exemplified in *Drosophila* male germline stem cells (GSCs). In these cells, naturally delayed lagging-strand synthesis can result from an approximately 50% reduction in lagging-strand polymerase levels [50]. Consequently, at individual replication forks, parental histones are preferentially recycled onto the leading strand, whereas new histones are incorporated onto the lagging strand (figure 1B) [50,67]. Early-stage germ cells, including GSCs, also exhibit a high incidence of coordinated fork movement, which further reinforces sister chromatid-wide histone asymmetry [67]. During mitosis, asymmetric sister centromeres and asynchronous spindle dynamics cooperate to ensure biased segregation of sister chromatids with distinct histone inheritance to the two daughter cells [68,69].

Histone inheritance asymmetry has also been reported in *Drosophila* intestinal stem cells (ISCs) and female GSCs. In the midgut, asymmetrically dividing ISCs display asymmetric histone inheritance, whereas symmetrically dividing ISCs inherit parental histone symmetrically, indicating that histone asymmetry is associated with cell-division mode rather than stem cell identity [70]. In female GSCs, gene-specific asymmetry in histone inheritance has been detected at genomic loci associated with either stemness or differentiation genes, suggesting that epigenetic asymmetry may precede transcriptional changes during adult stem cell differentiation [71].

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Disruption of asymmetric histone inheritance can occur through either *cis* or *trans* mechanisms. In the *cis* case, expression of the mutant histone H3T3A (Thr3-to-Ala mutation) disrupts asymmetric histone inheritance in male GSCs and female ISCs, resulting in defective stem cell maintenance and differentiation [70,72]. In the *trans* case, disruption of asynchronous spindle dynamics in male GSCs abolishes biased sister chromatid segregation without disrupting the initial establishment of the histone asymmetry during DNA replication [68].

3.2. Histone asymmetry in mammalian systems

Asymmetric parental histone inheritance has also been reported in mammalian systems. One example is the mouse olfactory epithelium, where horizontal basal stem cells asymmetrically inherit canonical histones H3 and H4, but not H2A–H2B, and also exhibit asymmetric inheritance of the replication-independent histone variant H3.3 [73]. These findings indicate that both DNA replication-coupled mechanisms governing canonical histone recycling and replication-independent mechanisms regulating histone variant deposition contribute to establishing epigenetic asymmetry in this system.

Evidence for regulated histone asymmetry has also been detected in cultured mESCs. Under standard culture conditions, parental histones display a slight bias towards the leading strand [15]. When asymmetric division is induced by localized signalling using Wnt3a-coated beads, parental H3 and H4, together with parental histone-enriched modifications such as H4K20me2/3, display enhanced asymmetry at replication forks compared with controls without Wnt3a induction [73]. Furthermore, single-cell multi-omic analyses reveal that daughter cells resulting from Wnt3a-induced asymmetric mESC division acquire distinct transcriptional programmes accompanied by differential enrichment of the repressive histone modification H3K27me3, whereas the active mark H3K4me3 remains largely unchanged [74]. Together, these findings suggest that extrinsic signals can likely modulate histone recycling dynamics during DNA replication, thereby promoting distinct epigenetic states in the resulting daughter cells.

3.3. Effects of asymmetric histone recycling on gene expression and cell fate

Asymmetric histone inheritance can regulate gene expression immediately following DNA replication. For example, the human silencing hub (HUSH) complex interacts with DNA polymerase ε to promote asymmetric deposition of H3K9me3 onto the leading strand [75]. Loss of the HUSH component TASOR abolishes this H3K9me3 asymmetry, resulting in derepression of LINE-1 elements, accumulation of DNA damage and subsequent cell death [75,76]. Because the leading strand becomes transcriptionally competent earlier than the lagging strand, it has been proposed that preferential deposition of H3K9me3 onto the leading strand serves to rapidly repress LINE-1 transcription until silencing can be established on both sister chromatids through coordinated 'reader–writer' mechanisms.

In addition to parental histone recycling, asymmetric deposition of newly synthesized histones may also contribute to distinct chromatin states and subsequent gene expression changes. Chromatin assembly factor 1 (CAF-1), together with Asf-1, deposits new histones onto nascent DNA strands behind the replication fork [77–79]. Because CAF-1 is recruited by PCNA, it has been proposed that asymmetric PCNA occupancy between the leading and lagging strands could contribute to asymmetric incorporation of new histones [77]. More broadly, perturbation of CAF-1 function has profound effects on cell fate. For example, loss of CAF-1 causes cell cycle defects, defective cellular differentiation in zebrafish, and disruption of bilateral asymmetry during *C. elegans* development [80,81]. Conversely, partial suppression of CAF-1 by RNAi in mESCs enhances cellular plasticity and promotes reprogramming towards a totipotent 2-cell-like state [82] (reviewed in [83]). These seemingly opposite results likely reflect the degree of functional perturbation. Although a complete loss of CAF-1 severely disrupts chromatin assembly, partial reduction of CAF-1 by RNAi knockdown could allow replication to proceed while altering replication dynamics, including reduced fork speed, a feature associated with early embryogenesis [84]. These studies underscore that cell fate is highly sensitive to the extent of replisome perturbation, which will be discussed further below.

Similar examples demonstrate the extent to which asymmetric histone incorporation and inheritance can be required for proper gene expression and cell fate. In developing *C. elegans*, the histone chaperone activity of the CMG complex is required for proper cell fate specification following asymmetric division and may be tied to asymmetric epigenetic states at the pro-apoptotic *egl-1* locus following replication [85]. In mouse horizontal basal cells in olfactory epithelium, asymmetric inheritance of the histone variant H3.3 is associated with asynchronous transcriptional reactivation and unequal recruitment of the stem cell determinant p63 transcription factor in daughter cells [73]. Inheritance of asymmetric chromatin states can also serve genome integrity: in human cells, damaged DNA is preferentially segregated to one daughter cell through post-replicative incorporation of new histones that can distinguish damaged sister chromatids [86].

Histone asymmetry can also be experimentally induced by modulating replication components. Partial reduction of primase-polα levels or activities in differentiating cells of the *Drosophila* germline generates local asymmetric histone recycling through delayed lagging strand synthesis [50]. This manipulation recreates the spatial separation of old and new histones at replication forks in differentiating non-stem cells, a feature normally observed in stem cells of the same lineage. Similar effects can be achieved using low concentrations of a chemical inhibitor targeting the catalytic subunit of polα [50]. Importantly, these experiments rely on partial reduction of primase-polα activity through heterozygous mutation or reversible chemical inhibition rather than complete loss of function. Because lagging strand synthesis requires repeated initiation of Okazaki fragments, modest reduction of primase-polα activity selectively alters lagging-strand replication dynamics while preserving overall DNA replication [87]. This

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differs fundamentally from complete loss-of-function mutations, which severely disrupt DNA replication. Thus, the biological consequences of manipulating certain replication factors depend critically on the extent and context of functional perturbation.

The ability to remodel chromatin in differentiating non-stem cells towards a stem cell-like state highlights the potential of controlled modulation of DNA replication as a powerful means to manipulate cell fate, especially given the conservation of replication proteins and processes. It has been reported that partial reduction of primase-polα levels or activities across *Drosophila*, *C. elegans* and mammalian cells improves fertility, enhances tissue regeneration and promotes cellular reprogramming [88], suggesting that controlled modulation of histone recycling may represent a broad strategy for enhancing cellular plasticity and organismal fitness.

Beyond immediate effects on gene expression, asymmetric histone recycling can also result in different nucleosome densities between sister chromatids following replication. Several studies suggest that preferential recycling of parental histones to one strand transiently reduces nucleosome density on the opposite strand, indicating that new histone deposition does not always immediately restore nucleosome density [15,46,67]. Consequently, such low-density chromatin containing predominantly new histones may provide a permissive environment to establish a new epigenome for a changing cell fate (figure 1B,C). In some cases, this could have detrimental effects (see §§2.5 and 3.4). However, in a developmental context, this may represent an efficient mechanism for selectively resetting the epigenome on one sister chromatid while preserving the parental chromatin state on the other. In *Drosophila* male GSCs, the nucleosome density difference between sister chromatids creates distinct chromatin accessibility that preferentially recruits the pre-replication factor Cdc6 to the sister chromatid with lower nucleosome density. This asymmetric Cdc6 loading results in asynchronous DNA replication initiation in the two resulting daughter cells [69] (reviewed in [89]), and it contributes to distinct interchromosomal interactions at the stemness gene *stat92e* [90]. These findings demonstrate that asymmetric histone inheritance can influence not only gene expression but also subsequent cell cycle progression and genome organization.

Collectively, these studies demonstrate that asymmetric histone inheritance is a versatile mechanism for regulating gene expression, chromatin organization and cell fate (figure 1). Depending on the context, this asymmetry may occur globally between sister chromatids [67,70,91], or it may be restricted to specific genomic regions or histone modifications [71,74,75,92]. Continued applications of techniques such as eSPAN and SCAR-seq (table 1), together with high-resolution imaging approaches suitable for rare cell populations, will help uncover when, where and how asymmetric histone inheritance is established and determine whether controlled modulation of histone recycling can be used to promote tissue maintenance and regeneration, cellular reprogramming and organismal fitness.

3.4. Asymmetric histone recycling as a competitive advantage for cancer cells

Although asymmetric histone recycling likely evolved to promote developmental plasticity and cellular diversity, dysregulated histone recycling can be exploited by tumour cells. Epigenetic dysregulation and genome instability are hallmarks of cancer cells (reviewed in [93,94]). Defects in parental histone recycling can contribute to both processes by disrupting the faithful inheritance of the epigenetic landscape. In particular, impaired histone recycling has been linked to reduced H3K27me3, leading to ectopic expression of proliferation genes during tumourigenesis [95,96]. Mutation of the histone-binding domain of Mcm2 in breast cancer cells, for example, impairs parental histone recycling and disrupts the genome-wide distribution of both H3K27me3 and H3K4me3 [96]. These findings suggest that altered histone recycling can reshape the epigenetic landscape in ways that favour malignant transformation.

The histone chaperone Asf1 provides another example of the importance of maintaining balanced nucleosome reassembly during DNA replication [42,43,97,98]. In *C. elegans*, mutation of the Asf1 homologue *unc-85* shortens lifespan and elevates one-carbon metabolism, a metabolic state frequently associated with cancer cells [99,100]. Conversely, Asf1 is overexpressed in cancer cells of diverse origins, including lung adenocarcinoma, cervical cancer and hepatocellular carcinoma, where it promotes proliferation, whereas inhibition of Asf1 suppresses tumour growth by inducing DNA damage and apoptosis [101–103]. These findings suggest that histone chaperones function within an optimal range of activity. Both insufficient and excessive histone chaperone function can perturb chromatin organization, disrupt expression of tumour suppressors or oncogenes, and alter cellular fitness.

Taken together, these studies highlight the importance of balanced replication-coupled chromatin assembly for tumour suppression and organismal health. Because the benefits and drawbacks of symmetric and asymmetric histone recycling are highly context dependent, strategies designed to manipulate histone recycling therapeutically must carefully balance the benefits of enhanced epigenetic plasticity against the potential risk of promoting oncogenic transformation. This consideration is particularly relevant because many common chemotherapeutic agents target DNA replication proteins that also participate in parental histone recycling, including DNA polymerases [104]. Understanding how these treatments alter epigenetic inheritance in both normal and malignant cells may help minimize unintended chromatin remodelling and improve therapeutic outcomes.

Although cancer provides a clear disease context in which histone recycling has been implicated, epigenetic dysregulation contributes to a plethora of other disorders. Altered histone modification landscapes have been reported in neurodegenerative disorders such as Alzheimer's disease [105,106] and metabolic disorders including type 2 diabetes [107], as well as in cardiovascular, inflammatory, renal and skeletal muscle diseases. In proliferative cells, altered histone recycling could amplify these epigenetic abnormalities. Conversely, the transiently permissive chromatin state following asymmetric histone incorporation may also provide an opportunity to re-establish appropriate epigenetic landscapes. Defining how histone recycling contributes to disease progression will therefore be important for identifying new therapeutic strategies that target epigenetic inheritance rather than individual histone modifications.

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4. Concluding remarks and future perspectives

The studies discussed in this review demonstrate that parental histone recycling at the replication fork is generally balanced and faithful in proliferating cells that maintain cellular identity, yet this process can be selectively reconfigured to promote asymmetric histone incorporation during lineage specification and cell fate changes. These distinct modes of histone recycling reflect the fundamental balance between epigenetic stability and plasticity that underlies multicellular organismal development. Rather than serving solely as a mechanism for preserving chromatin states, the DNA replication machinery is increasingly emerging as a dynamic regulator of epigenetic inheritance that can either maintain or remodel cell identity depending on developmental context.

Because most mechanistic studies of histone recycling have been performed in homogeneous cell populations or cultured cell lines, the nuances of histone recycling in multicellular organisms present an area ripe for research. Defining the extent to which histone recycling is modulated across different tissues, developmental stages and regenerative processes will be essential for translating these discoveries into clinical applications. Specifically, if replicative cells *in vivo* do not always recycle histones with the high fidelity observed in cultured cells, therapeutic treatments targeting DNA replication could have previously unrecognized consequences as well as new opportunities for intervention. Additionally, controlled establishment of a naive epigenetic environment through regulated histone recycling could hold promise for cellular reprogramming, tissue repair and regenerative medicine.

The remarkable evolutionary conservation of DNA replication components further suggests that the principles governing histone recycling may extend well beyond yeast and animal model systems. Indeed, studies in the flowering plant *Arabidopsis* have demonstrated similar mechanisms of parental histone incorporation and related developmental phenotypes in mutants [108,109]. These findings suggest that replication-coupled histone recycling is deeply conserved and raise the possibility that manipulating this process could improve plant development, crop yields or agricultural resilience. Meanwhile, plant systems may uncover novel epigenetic mechanisms that are broadly relevant to animal development and regeneration.

The field of histone recycling is likely on the precipice of an explosion of major advances. Recent reconstitution of this process *in vitro* now enables direct mechanistic dissection of replication-coupled histone recycling under defined conditions [110]. In parallel, genomic approaches such as eSPAN, SCAR-seq and other emerging techniques have already significantly advanced our understanding of histone recycling dynamics at the replication fork in yeast or cultured cells (table 1) [15,37,111]. Continued refinement of these approaches for rare cell populations, developing tissues and experiments requiring high temporal resolution will be essential for understanding how histone recycling is regulated in physiological contexts. Together, these advances promise to establish histone recycling as a central mechanism linking DNA replication, epigenetic inheritance and cell-fate determination, while opening new opportunities to manipulate chromatin states in development, regeneration, agriculture and human disease.

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Author's contributions. B.E.M.D.: conceptualization, formal analysis, funding acquisition, investigation, project administration, supervision, visualization, writing—original draft, writing—review and editing; A.C.P.: conceptualization, formal analysis, investigation, writing—original draft, writing—review and editing; X.C.: conceptualization, funding acquisition, project administration, supervision, writing—original draft, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. The authors have a patent filed through the Johns Hopkins Technology Ventures office (US 63/565742). This patent is related to published work that is discussed in this paper (PMID: 40020063, 39345551). B.E.M.D. and X.C. are inventors on this patent. The authors declare that they have no other competing interests.

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References

1. Franklin RE, Gosling RG. 1953 Molecular configuration in sodium thymonucleate. *Nature* **171**, 740–741. (doi:10.1038/171740a0)
2. Hershey AD, Chase M. 1952 Independent functions of viral protein and nucleic acid in growth of bacteriophage. *J. Gen. Physiol.* **36**, 39–56. (doi:10.1085/jgp.36.1.39)
3. Wilkins MHF, Stokes AR, Wilson HR. 1953 Molecular structure of nucleic acids: molecular structure of deoxypentose nucleic acids. *Nature* **171**, 738–740. (doi:10.1038/171738a0)
4. Meselson M, Stahl FW. 1958 The replication of DNA in *Escherichia coli*. *Proc. Natl Acad. Sci. USA* **44**, 671–682. (doi:10.1073/pnas.44.7.671)
5. Watson JD, Crick FHC. 1953 Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature* **171**, 737–738. (doi:10.1038/171737a0)
6. Hulton CSJ *et al.* 1990 Histone-like protein H1 (H-NS), DNA supercoiling, and gene expression in bacteria. *Cell* **63**, 631–642. (doi:10.1016/0092-8674(90)90458-q)
7. Riggs AD. 1975 X inactivation, differentiation, and DNA methylation. *Cytogenet. Cell. Genet.* **14**, 9–25. (doi:10.1159/000130315)
8. Holliday R, Pugh JE. 1975 DNA modification mechanisms and gene activity during development. *Science* **187**, 226–232. (doi:10.1126/science.187.4173.226)
9. Allfrey VG, Faulkner R, Mirsky AE. 1964 Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis. *Proc. Natl Acad. Sci. USA* **51**, 786–794. (doi:10.1073/pnas.51.5.786)
10. Strahl BD, Allis CD. 2000 The language of covalent histone modifications. *Nature* **403**, 41–45. (doi:10.1038/47412)
11. Cedar H, Bergman Y. 2009 Linking DNA methylation and histone modification: patterns and paradigms. *Nat. Rev. Genet.* **10**, 295–304. (doi:10.1038/nrg2540)

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12. Du W, Shi G,Li Z,Zhu B,Jia S,Li Q,Zhang Z. 2022 Mechanisms of chromatin-based epigenetic inheritance. *Sci. China Life Sci.* **65**, 2162–2190. (doi:10.1007/s11427-022-2120-1)
13. Millan-Zambrano G, Burton A, Bannister AJ, Schneider R. 2022 Histone post-translational modifications—cause and consequence of genome function. *Nat. Rev. Genet.* **23**, 563–580. (doi:10.1038/s41576-022-00468-7)
14. Xiong J, Zhu B. 2025 Epigenetic preparation of future gene induction kinetics. *Annu. Rev. Genet.* **59**, 25–49. (doi:10.1146/annurev-genet-012825-093148)
15. Petryk N, Dalby M, Wenger A, Stromme CB, Strandsby A, Andersson R, Groth A. 2018 MCM2 promotes symmetric inheritance of modified histones during DNA replication. *Science* **361**, 1389–1392. (doi:10.1126/science.aau0294)
16. Gan H, Serra-Cardona A, Hua X, Zhou H, Labib K, Yu C, Zhang Z. 2018 The Mcm2-Ctf4-Polα axis facilitates parental histone H3-H4 transfer to lagging strands. *Mol. Cell* **72**, 140–151. (doi:10.1016/j.molcel.2018.09.001)
17. Mühlen D, Li X, Dovgusha O, Jäckle H, Günesdogan U. 2023 Recycling of parental histones preserves the epigenetic landscape during embryonic development. *Sci. Adv.* **9**, eadd6440. (doi:10.1126/sciadv.add6440)
18. Deshmukh AL, Kumar C, Singh DK, Maurya P, Banerjee D. 2016 Dynamics of replication proteins during lagging strand synthesis: a crossroads for genomic instability and cancer. *DNA Repair (Amst)* **42**, 72–81. (doi:10.1016/j.dnarep.2016.04.010)
19. Sidoli S *et al.* 2019 One minute analysis of 200 histone posttranslational modifications by direct injection mass spectrometry. *Genome Res.* **29**, 978–987. (doi:10.1101/gr.247353.118)
20. Charlton SJ *et al.* 2024 The fork protection complex promotes parental histone recycling and epigenetic memory. *Cell* **187**, 5029–5047. (doi:10.1016/j.cell.2024.07.017)
21. Petruk S, Black KL, Kovermann SK, Brock HW, Mazo A. 2013 Stepwise histone modifications are mediated by multiple enzymes that rapidly associate with nascent DNA during replication. *Nat. Commun.* **4**, 2841. (doi:10.1038/ncomms3841)
22. Flury V, Reverón-Gómez N, Alcaraz N, Stewart-Morgan KR, Wenger A, Klose RJ, Groth A. 2023 Recycling of modified H2A-H2B provides short-term memory of chromatin states. *Cell* **186**, 1050–1065. (doi:10.1016/j.cell.2023.01.007)
23. Kimura H. 2005 Histone dynamics in living cells revealed by photobleaching. *DNA Repair (Amst)* **4**, 939–950. (doi:10.1016/j.dnarep.2005.04.012)
24. Clément C *et al.* 2018 High-resolution visualization of H3 variants during replication reveals their controlled recycling. *Nat. Commun.* **9**, 3181. (doi:10.1038/s41467-018-05697-1)
25. Xu X, Duan S, Hua X, Li Z, He R, Zhang Z. 2022 Stable inheritance of H3.3-containing nucleosomes during mitotic cell divisions. *Nat. Commun.* **13**, 2514. (doi:10.1038/s41467-022-30298-4)
26. Alabert C, Barth TK, Reverón-Gómez N, Sidoli S, Schmidt A, Jensen ON, Imhof A, Groth A. 2015 Two distinct modes for propagation of histone PTMs across the cell cycle. *Genes Dev.* **29**, 585–590. (doi:10.1101/gad.256354.114)
27. Serra-Cardona A, Zhang Z. 2018 Replication-coupled nucleosome assembly in the passage of epigenetic information and cell identity. *Trends Biochem. Sci.* **43**, 136–148. (doi:10.1016/j.tibs.2017.12.003)
28. Flury V, Groth A. 2024 Safeguarding the epigenome through the cell cycle: a multitasking game. *Curr. Opin. Genet. Dev.* **85**, 102161. (doi:10.1016/j.gde.2024.102161)
29. Yu J, Moazed D. In press. Epigenetic inheritance through replication-coupled parental histone recycling. *Annu. Rev. Cell Dev. Biol.* **42**. (doi:10.1146/annurev-cellbio-111524-044608)
30. Li Z, Zhang Z. 2025 A tale of two strands: decoding chromatin replication through strand-specific sequencing. *Mol. Cell* **85**, 238–261. (doi:10.1016/j.molcel.2024.10.035)
31. Skene PJ, Henikoff S. 2017 An efficient targeted nuclease strategy for high-resolution mapping of DNA binding sites. *eLife* **6**, e21856. (doi:10.7554/eLife.21856)
32. Kaya-Okur HS, Wu SJ, Codomo CA, Pledger ES, Bryson TD, Henikoff JG, Ahmad K, Henikoff S. 2019 CUT&Tag for efficient epigenomic profiling of small samples and single cells. *Nat. Commun.* **10**, 1930. (doi:10.1038/s41467-019-09982-5)
33. Li Z, Hua X, Serra-Cardona A, Xu X, Zhang Z. 2021 Efficient and strand-specific profiling of replicating chromatin with enrichment and sequencing of protein-associated nascent DNA in mammalian cells. *Nat. Protoc.* **16**, 2698–2721. (doi:10.1038/s41596-021-00520-6)
34. Petryk N, Reverón-Gómez N, González-Aguilera C, Dalby M, Andersson R, Groth A. 2021 Genome-wide and sister chromatid-resolved profiling of protein occupancy in replicated chromatin with ChOR-seq and SCAR-seq. *Nat. Protoc.* **16**, 4446–4493. (doi:10.1038/s41596-021-00585-3)
35. Petryk N, Kahli M, d'Aubenton-Carafa Y, Jaszczyszyn Y, Shen Y, Silvain M, Thermes C, Chen C-L, Hyrien O. 2016 Replication landscape of the human genome. *Nat. Commun.* **7**, 10208. (doi:10.1038/ncomms10208)
36. Wooten M, Li Y, Snedeker J, Nizami ZF, Gall JG, Chen X. 2020 Superresolution imaging of chromatin fibers to visualize epigenetic information on replicative DNA. *Nat. Protoc.* **15**, 1188–1208. (doi:10.1038/s41596-019-0283-y)
37. Li Z *et al.* 2020 DNA polymerase α interacts with H3-H4 and facilitates the transfer of parental histones to lagging strands. *Sci. Adv.* **6**, eabb5820. (doi:10.1126/sciadv.abb5820)
38. Kornberg RD, Lorch Y. 1999 Twenty-five years of the nucleosome, fundamental particle of the eukaryote chromosome. *Cell* **98**, 285–294. (doi:10.1016/s0092-8674(00)81958-3)
39. Safaric B, Chacin E, Scherr MJ, Rajappa L, Gebhardt C, Kurat CF, Cordes T, Duderstadt KE. 2022 The fork protection complex recruits FACT to reorganize nucleosomes during replication. *Nucleic Acids Res.* **50**, 1317–1334. (doi:10.1093/nar/gkac005)
40. Wang X *et al.* 2023 The N-terminus of Spt16 anchors FACT to MCM2-7 for parental histone recycling. *Nucleic Acids Res.* **51**, 11549–11567. (doi:10.1093/nar/gkad846)
41. Li N *et al.* 2024 Parental histone transfer caught at the replication fork. *Nature* **627**, 890–897. (doi:10.1038/s41586-024-07152-2)
42. Shan Z, Zhang Y, Bu J, Li H, Zhang Z, Xiong J, Zhu B. 2023 The patterns and participants of parental histone recycling during DNA replication in *Saccharomyces cerevisiae*. *Sci. China Life Sci.* **66**, 1600–1614. (doi:10.1007/s11427-022-2267-6)
43. Huang H, Strømme CB, Saredi G, Hödl M, Strandsby A, González-Aguilera C, Chen S, Groth A, Patel DJ. 2015 A unique binding mode enables MCM2 to chaperone histones H3–H4 at replication forks. *Nat. Struct. Mol. Biol.* **22**, 618–626. (doi:10.1038/nsmb.3055)
44. Nagae F, Murayama Y, Terakawa T. 2024 Molecular mechanism of parental H3/H4 recycling at a replication fork. *Nat. Commun.* **15**, 9485. (doi:10.1038/s41467-024-53187-4)
45. Richet N *et al.* 2015 Structural insight into how the human helicase subunit MCM2 may act as a histone chaperone together with ASF1 at the replication fork. *Nucleic Acids Res.* **43**, 1905–1917. (doi:10.1093/nar/gkv021)
46. Yu C *et al.* 2018 A mechanism for preventing asymmetric histone segregation onto replicating DNA strands. *Science* **361**, 1386–1389. (doi:10.1126/science.aat8849)
47. Bellelli R, Belan O, Pye VE, Clement C, Maslen SL, Skehel JM, Cherepanov P, Almouzni G, Boulton SJ. 2018 POLE3-POLE4 is a histone H3-H4 chaperone that maintains chromatin integrity during DNA replication. *Mol. Cell* **72**, 112–126. (doi:10.1016/j.molcel.2018.08.043)
48. Xu Z *et al.* 2023 Synergism between CMG helicase and leading strand DNA polymerase at replication fork. *Nat. Commun.* **14**, 5849. (doi:10.1038/s41467-023-41506-0)
49. Ercilla A. 2020 Physiological tolerance to ssDNA enables strand uncoupling during DNA replication. *Cell Rep.* **30**, 2416–2429. (doi:10.1016/j.celrep.2020.01.067)

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50. Davis BEM, Snedeker J, Ranjan R, Wooten M, Barton SS, Blundon J, Chen X. 2025 Increased levels of lagging strand polymerase α in an adult stem cell lineage affect replication-coupled histone incorporation. *Sci. Adv.* **11**, eadu6799. (doi:10.1126/sciadv.adu6799)
51. Tian C *et al.* 2024 DNA polymerase delta governs parental histone transfer to DNA replication lagging strand. *Proc. Natl Acad. Sci. USA* **121**, e2400610121. (doi:10.1073/pnas.2400610121)
52. Zhou Z-X, Lujan SA, Burkholder AB, Garbacz MA, Kunkel TA. 2019 Roles for DNA polymerase δ in initiating and terminating leading strand DNA replication. *Nat. Commun.* **10**, 3992. (doi:10.1038/s41467-019-11995-z)
53. Johnson RE, Klassen R, Prakash L, Prakash S. 2015 A major role of DNA polymerase δ in replication of both the leading and lagging DNA strands. *Mol. Cell* **59**, 163–175. (doi:10.1016/j.molcel.2015.05.038)
54. Miyabe I, Kunkel TA, Carr AM. 2011 The major roles of DNA polymerases epsilon and delta at the eukaryotic replication fork are evolutionarily conserved. *PLoS Genet.* **7**, e1002407. (doi:10.1371/journal.pgen.1002407)
55. Fumasoni M, Zwicky K, Vanoli F, Lopes M, Branzei D. 2015 Error-free DNA damage tolerance and sister chromatid proximity during DNA replication rely on the Polα/Primase/Ctf4 complex. *Mol. Cell* **57**, 812–823. (doi:10.1016/j.molcel.2014.12.038)
56. Jones ML, Aria V, Baris Y, Yeeles JTP. 2023 How Pol α-primase is targeted to replisomes to prime eukaryotic DNA replication. *Mol. Cell* **83**, 2911–2924. (doi:10.1016/j.molcel.2023.06.035)
57. Alcasabas AA *et al.* 2001 Mrc1 transduces signals of DNA replication stress to activate Rad53. *Nat. Cell Biol.* **3**, 958–965. (doi:10.1038/ncb1101-958)
58. Tanaka K, Russell P. 2001 Mrc1 channels the DNA replication arrest signal to checkpoint kinase Cds1. *Nat. Cell Biol.* **3**, 966–972. (doi:10.1038/ncb1101-966)
59. Nitani N, Nakamura K-I, Nakagawa C, Masukata H, Nakagawa T. 2006 Regulation of DNA replication machinery by Mrc1 in fission yeast. *Genetics* **174**, 155–165. (doi:10.1534/genetics.106.060053)
60. Yu J *et al.* 2024 A replisome-associated histone H3-H4 chaperone required for epigenetic inheritance. *Cell* **187**, 5010–5028. (doi:10.1016/j.cell.2024.07.006)
61. Foltman M, Evrin C, De Piccoli G, Jones RC, Edmondson RD, Katou Y, Nakato R, Shirahige K, Labib K. 2013 Eukaryotic replisome components cooperate to process histones during chromosome replication. *Cell Rep.* **3**, 892–904. (doi:10.1016/j.celrep.2013.02.028)
62. Wen Q *et al.* 2023 Symmetric inheritance of parental histones contributes to safeguarding the fate of mouse embryonic stem cells during differentiation. *Nat. Genet.* **55**, 1555–1566. (doi:10.1038/s41588-023-01477-w)
63. Jeronimo C, Poitras C, Robert F. 2019 Histone recycling by FACT and Spt6 during transcription prevents the scrambling of histone modifications. *Cell Rep.* **28**, 1206–1218. (doi:10.1016/j.celrep.2019.06.097)
64. Kollenstart L, Biran A, Alcaraz N, Reverón-Gómez N, Solis-Mezarino V, Völker-Albert M, Jenkinson F, Flury V, Groth A. 2025 Disabling leading and lagging strand histone transmission results in parental histones loss and reduced cell plasticity and viability. *Sci. Adv.* **11**, eadr1453. (doi:10.1126/sciadv.adr1453)
65. Wenger A *et al.* 2023 Symmetric inheritance of parental histones governs epigenome maintenance and embryonic stem cell identity. *Nat. Genet.* **55**, 1567–1578. (doi:10.1038/s41588-023-01476-x)
66. Karri S, Yang Y, Zhou J, Dickinson Q, Jia J, Huang Y, Wang Z, Gan H, Yu C. 2024 Defective transfer of parental histone decreases frequency of homologous recombination by increasing free histone pools in budding yeast. *Nucleic Acids Res.* **52**, 5138–5151. (doi:10.1093/nar/gkae205)
67. Wooten M *et al.* 2019 Asymmetric histone inheritance via strand-specific incorporation and biased replication fork movement. *Nat. Struct. Mol. Biol.* **26**, 732–743. (doi:10.1038/s41594-019-0269-z)
68. Ranjan R, Snedeker J, Chen X. 2019 Asymmetric centromeres differentially coordinate with mitotic machinery to ensure biased sister chromatid segregation in germline stem cells. *Cell Stem Cell* **25**, 666–681. (doi:10.1016/j.stem.2019.08.014)
69. Ranjan R, Snedeker J, Wooten M, Chu C, Bracero S, Mouton T, Chen X. 2022 Differential condensation of sister chromatids acts with Cdc6 to ensure asynchronous S-phase entry in *Drosophila* male germline stem cell lineage. *Dev. Cell* **57**, 1102–1118. (doi:10.1016/j.devcel.2022.04.007)
70. Zion EH, Ringwalt D, Rinaldi K, Kahney EW, Li Y, Chen X. 2023 Old and newly synthesized histones are asymmetrically distributed in *Drosophila* intestinal stem cell divisions. *EMBO Rep.* **24**, EMBR202256404. (doi:10.15252/embr.202256404)
71. Kahney EW, Zion EH, Sohn L, Viets-Layng K, Johnston R, Chen X. 2021 Characterization of histone inheritance patterns in the *Drosophila* female germline. *EMBO Rep.* **22**, EMBR202051530. (doi:10.15252/embr.202051530)
72. Xie J, Wooten M, Tran V, Chen B-C, Pozmanter C, Simbolon C, Betzig E, Chen X. 2015 Histone H3 threonine phosphorylation regulates asymmetric histone inheritance in the *Drosophila* male germline. *Cell* **163**, 920–933. (doi:10.1016/j.cell.2015.10.002)
73. Ma B *et al.* 2026 Asymmetric histone inheritance regulates olfactory stem cell fates during regeneration. *Nat. Commun.* **17**, 4361. (doi:10.1038/s41467-026-70987-y)
74. Sun Z, Tang Y, Zhang Y, Fang Y, Jia J, Zeng W, Fang D. 2021 Joint single-cell multiomic analysis in Wnt3a induced asymmetric stem cell division. *Nat. Commun.* **12**, 5941. (doi:10.1038/s41467-021-26203-0)
75. Li Z *et al.* 2023 Asymmetric distribution of parental H3K9me3 in S phase silences L1 elements. *Nature* **623**, 643–651. (doi:10.1038/s41586-023-06711-3)
76. Pinzon-Arteaga CA *et al.* 2024 TASOR expression in naive embryonic stem cells safeguards their developmental potential. *Cell Rep.* **43**, 114887. (doi:10.1016/j.celrep.2024.114887)
77. Shibahara K-I, Stillman B. 1999 Replication-dependent marking of DNA by PCNA facilitates CAF-1-coupled inheritance of chromatin. *Cell* **96**, 575–585. (doi:10.1016/s0092-8674(00)80661-3)
78. Liu C-P *et al.* 2023 Structural insights into histone binding and nucleosome assembly by chromatin assembly factor-1. *Science* **381**, eadd8673. (doi:10.1126/science.add8673)
79. Rouillon C *et al.* 2023 CAF-1 deposits newly synthesized histones during DNA replication using distinct mechanisms on the leading and lagging strands. *Nucleic Acids Res.* **51**, 3770–3792. (doi:10.1093/nar/gkad171)
80. Fischer S, Prijkhozhij S, Rau MJ, Neumann CJ. 2007 Mutation of zebrafish caf-1b results in S phase arrest, defective differentiation, and p53-mediated apoptosis during organogenesis. *Cell Cycle* **6**, 2962–2969. (doi:10.4161/cc.6.23.4950)
81. Nakano S, Stillman B, Horvitz HR. 2011 Replication-coupled chromatin assembly generates a neuronal bilateral asymmetry in *C. elegans*. *Cell* **147**, 1525–1536. (doi:10.1016/j.cell.2011.11.053)
82. Ishiuchi T, Enriquez-Gasca R, Mizutani E, Bošković A, Ziegler-Birling C, Rodriguez-Terrones D, Wakayama T, Vaquerizas JM, Torres-Padilla M-E. 2015 Early embryonic-like cells are induced by downregulating replication-dependent chromatin assembly. *Nat. Struct. Mol. Biol.* **22**, 662–671. (doi:10.1038/nsmb.3066)

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83. Cheloufi S, Hochedlinger K. 2017 Emerging roles of the histone chaperone CAF-1 in cellular plasticity. *Curr. Opin. Genet. Dev.* **46**, 83–94. (doi:10.1016/j.gde.2017.06.004)
84. Nakatani T *et al.* 2022 DNA replication fork speed underlies cell fate changes and promotes reprogramming. *Nat. Genet.* **54**, 318–327. (doi:10.1038/s41588-022-01023-0)
85. Memar N, Sherrard R, Sethi A, Fernandez CL, Schmidt H, Lambie EJ, Poole RJ, Schnabel R, Conradt B. 2024 The replicative helicase CMG is required for the divergence of cell fates during asymmetric cell division in vivo. *Nat. Commun.* **15**, 9399. (doi:10.1038/s41467-024-53715-2)
86. Ferrand J, Dabin J, Chevallier O, Kane-Charvin M, Kupai A, Hrit J, Rothbart SB, Polo SE. 2025 Mitotic chromatin marking governs the segregation of DNA damage. *Nat. Commun.* **16**, 746. (doi:10.1038/s41467-025-56090-8)
87. Lynch L, Chistol G. 2025 Eukaryotic lagging strand synthesis is distributive. *bioRxiv*. (doi:10.1101/2025.09.17.676973)
88. Ranjan R *et al.* 2024 Modulating DNA polα enhances cell reprogramming across species. *bioRxiv*. (doi:10.1101/2024.09.19.613993)
89. Ranjan R, Chen X. 2022 Mitotic drive in asymmetric epigenetic inheritance. *Biochem. Soc. Trans.* **50**, 675–688. (doi:10.1042/BST20200267)
90. Antel M, Raj R, Masoud MYG, Pan Z, Li S, Mellone BG, Inaba M. 2022 Interchromosomal interaction of homologous *Stat92E* alleles regulates transcriptional switch during stem-cell differentiation. *Nat. Commun.* **13**, 3981. (doi:10.1038/s41467-022-31737-y)
91. Tran V, Lim C, Xie J, Chen X. 2012 Asymmetric division of *Drosophila* male germline stem cell shows asymmetric histone distribution. *Science* **338**, 679–682. (doi:10.1126/science.1226028)
92. Ma B *et al.* 2020 Differential histone distribution patterns in induced asymmetrically dividing mouse embryonic stem cells. *Cell Rep.* **32**, 108003. (doi:10.1016/j.celrep.2020.108003)
93. Yu X, Zhao H, Wang R, Chen Y, Ouyang X, Li W, Sun Y, Peng A. 2024 Cancer epigenetics: from laboratory studies and clinical trials to precision medicine. *Cell Death Discov.* **10**, 28. (doi:10.1038/s41420-024-01803-z)
94. Negrini S, Gorgoulis VG, Halazonetis TD. 2010 Genomic instability—an evolving hallmark of cancer. *Nat. Rev. Mol. Cell Biol.* **11**, 220–228. (doi:10.1038/nrm2858)
95. Gaggioli V *et al.* 2023 Dynamic de novo heterochromatin assembly and disassembly at replication forks ensures fork stability. *Nat. Cell Biol.* **25**, 1017–1032. (doi:10.1038/s41556-023-01167-z)
96. Tian C *et al.* 2023 Impaired histone inheritance promotes tumor progression. *Nat. Commun.* **14**, 3429. (doi:10.1038/s41467-023-39185-y)
97. Mello JA, Silljé HHW, Roche DMJ, Kirschner DB, Nigg EA, Almouzni G. 2002 Human Asf1 and CAF-1 interact and synergize in a repair-coupled nucleosome assembly pathway. *EMBO Rep.* **3**, 329–334. (doi:10.1093/embo-reports/kvf068)
98. Smith S, Stillman B. 1991 Stepwise assembly of chromatin during DNA replication in vitro. *EMBO J.* **10**, 971–980. (doi:10.1002/j.1460-2075.1991.tb08031.x)
99. Shrestha B, Nieminen AI, Matilainen O. 2024 Loss of the histone chaperone UNC-85/ASF1 inhibits the epigenome-mediated longevity and modulates the activity of one-carbon metabolism. *Cell Stress Chaperones* **29**, 392–403. (doi:10.1016/j.cstres.2024.04.003)
100. Ducker GS, Rabinowitz JD. 2017 One-carbon metabolism in health and disease. *Cell Metab.* **25**, 27–42. (doi:10.1016/j.cmet.2016.08.009)
101. Wu Y, Li X, Yu J, Björkholm M, Xu D. 2019 ASF1a inhibition induces p53-dependent growth arrest and senescence of cancer cells. *Cell Death Dis.* **10**, 76. (doi:10.1038/s41419-019-1357-z)
102. Liu X *et al.* 2020 ASF1B promotes cervical cancer progression through stabilization of CDK9. *Cell Death Dis.* **11**, 705. (doi:10.1038/s41419-020-02872-5)
103. Zhang W, Gao Z, Guan M, Liu N, Meng F, Wang G. 2021 ASF1B promotes oncogenesis in lung adenocarcinoma and other cancer types. *Front Oncol.* **11**, 731547. (doi:10.3389/fonc.2021.731547)
104. Gu L, Hickey RJ, Malkas LH. 2023 Therapeutic targeting of DNA replication stress in cancer. *Genes (Basel)* **14**, 1346. (doi:10.3390/genes14071346)
105. Nativio R *et al.* 2018 Dysregulation of the epigenetic landscape of normal aging in Alzheimer's disease. *Nat. Neurosci.* **21**, 497–505. (doi:10.1038/s41593-018-0101-9)
106. Williams JB, Cao Q, Wang W, Lee Y-H, Qin L, Zhong P, Ren Y, Ma K, Yan Z. 2023 Inhibition of histone methyltransferase Smyd3 rescues NMDAR and cognitive deficits in a tauopathy mouse model. *Nat. Commun.* **14**, 91. (doi:10.1038/s41467-022-35749-6)
107. Tu P, Huang B, Li M, Zhang Y, Bao S, Tu N, Yang Y, Lu J. 2022 Exendin-4 may improve type 2 diabetes by modulating the epigenetic modifications of pancreatic histone H3 in STZ-induced diabetic C57BL/6 J mice. *J. Physiol. Biochem.* **78**, 51–59. (doi:10.1007/s13105-021-00835-8)
108. Endo M *et al.* 2006 Increased frequency of homologous recombination and T-DNA integration in *Arabidopsis* CAF-1 mutants. *EMBO J.* **25**, 5579–5590. (doi:10.1038/sj.emboj.7601434)
109. Pratx L, Wendering P, Kappel C, Nikoloski Z, Bäurle I. 2023 Histone retention preserves epigenetic marks during heat stress-induced transcriptional memory in plants. *EMBO J.* **42**, EMBJ2023113595. (doi:10.15252/embj.2023113595)
110. Nagae F, Endo S, Murayama Y, Terakawa T. 2024 Minimal protein list for chromatin replication-coupled symmetric histone recycling revealed through *in vitro* reconstitution. *bioRxiv*. (doi:10.1101/2024.11.18.624094)
111. Ramachandran S, Henikoff S. 2016 Transcriptional regulators compete with nucleosomes post-replication. *Cell* **165**, 580–592. (doi:10.1016/j.cell.2016.02.062)

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