Cell Insight 3 (2024) 100195

Contents lists available at ScienceDirect

Cell Insight

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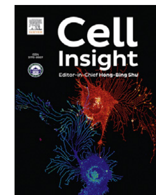
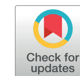


Review

Replication-coupled inheritance of chromatin states



Aoqun Song [a,b,c,d,1], Yunting Wang [a,1], Cuifang Liu [b,c], Juan Yu [b,c], Zixu Zhang [a,b,c,d], Liting Lan [b,c,d], Haiyan Lin [a,b,c], Jicheng Zhao [b,c,e,**], Guohong Li [a,b,c,d,*]

[a] *New Cornerstone Science Laboratory, Frontier Science Center for Immunology and Metabolism, Hubei Key Laboratory of Cell Homeostasis, College of Life Sciences, Taikang Center for Life and Medical Sciences, Wuhan University, Wuhan, 430072, China*
[b] *National Laboratory of Biomacromolecules, CAS Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, 100101, China*
[c] *Key Laboratory of Epigenetic Regulation and Intervention, Chinese Academy of Sciences, Beijing, 100101, China*
[d] *University of Chinese Academy of Sciences, Beijing, 100049, China*
[e] *Institute for Translational Medicine, The Affiliated Hospital of Qingdao University, College of Medicine, Qingdao University, Qingdao, 266021, China*

A R T I C L E I N F O

Keywords:
Chromatin
DNA replication
Epigenetic inheritance
Histone modifications

A B S T R A C T

During the development of eukaryote, faithful inheritance of chromatin states is central to the maintenance of cell fate. DNA replication poses a significant challenge for chromatin state inheritance because every nucleosome in the genome is disrupted as the replication fork passes. It has been found that many factors including DNA polymerases, histone chaperones, as well as, RNA Pol II and histone modifying enzymes coordinate spatially and temporally to maintain the epigenome during this progress. In this review, we provide a summary of the detailed mechanisms of replication-coupled nucleosome assembly and post-replication chromatin maturation, highlight the inheritance of chromatin states and epigenome during these processes, and discuss the future directions and challenges in this field.

1. Introduction

In eukaryotic cells, DNA is wrapped around histone octamer, which is composed of two H2A-H2B dimers and one $(H3\text{-}H4)_2$ tetramer, to form nucleosomes, the fundamental unit of chromatin (Arents & Moudrianakis, 1993; Davey et al., 2002). In the presence of linker histones, nucleosomes are further organized to interact with each other, forming 30 nm chromatin fibers (Chen et al., 2021; McGhee et al., 1983; Staynov et al., 1983; Woodcock et al., 1984). In the genome, DNA methylation and histone post-translational modifications (PTMs) play direct roles in gene regulation by marking the transcription status of local chromatin (Bannister & Kouzarides, 2011; Mattei et al., 2022). Consequently, chromatin regions can be divided into distinct domains, such as the repressive domain and active domain, according to their transcriptional activities (Dekker & Mirny, 2016; Escobar et al., 2019; Razin et al., 2007). Other factors such as histone variants, non-histone chromatin proteins, noncoding RNAs are also thought to regulate local transcription and gene expression (Bonev & Cavalli, 2016; Chen et al., 2016; Henikoff & Smith, 2015). Ultimately, the inheritable cell-specific chromatin states are established through the combination of multiple epigenetic information carriers described above.

Once established after early embryonic development, the chromatin states can be stably maintained during the long-term differentiation and development or dynamically altered in response to specific intra- and extracellular signaling stimuli. Such characteristics lead to the inheritability and plasticity of cell fate. The inheritance mode of chromatin states is critical for cell fate determination during the development of multicellular organisms. It has become increasingly clear that disorder in chromatin states drives developmental defects and tumorigenesis in many organs (Chan et al., 2013; Lewis et al., 2013). In proliferating cells, faithful inheritance of chromatin state faces a great challenge - DNA replication. During DNA replication, every nucleosome in the genome is disrupted ahead of the replication fork and rapidly re-assembled into nucleosomes on the nascent DNA strand via two distinct pathways,

* Corresponding author. New Cornerstone Science Laboratory, Frontier Science Center for Immunology and Metabolism, Hubei Key Laboratory of Cell Homeostasis, College of Life Sciences, Taikang Center for Life and Medical Sciences, Wuhan University, Wuhan, 430072, China.
** Corresponding author. National Laboratory of Biomacromolecules, CAS Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, 100101, China.
E-mail addresses: zjch@moon.ibp.ac.cn (J. Zhao), liguohong@whu.edu.cn, liguohong@sun5.ibp.ac.cn (G. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cellin.2024.100195
Received 5 May 2024; Received in revised form 5 August 2024; Accepted 5 August 2024
Available online 23 August 2024
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recycling of parental histones and de novo deposition of newly synthesized histones. This suggests that a large portion of epigenetic information in the parental chromatin is diluted or disturbed during DNA replication and it needs to be restored before the next S phase. Additionally, the faithful transmission of DNA methylation patterns during DNA replication also plays a pivotal role in preserving chromatin states (Ming et al., 2020; Wang et al., 2020; Xu & Corces, 2018), which is extensively discussed in previous reviews (Du et al., 2022; Espinosa-Martínez et al., 2024; Petryk et al., 2021). Therefore, this review mainly focuses on the dynamics of histones and chromatin structure during DNA replication.

A variety of regulators that facilitate the epigenetic inheritance of chromatin states can be generally divided into two groups: 1. Those function at the replication fork, which is enriched at the fork and interacts with the replisome components; 2. Those function after the passage of the replication, which is less enriched at the fork but critical to chromatin maturation after replication. In this review, we will summarize the most recent progress in understanding how chromatin states are inherited during the cell cycle. In the last section, we discuss the open questions and future direction of this field.

2. Epigenetic information transmission at the replication fork

During the S phase of cell cycle, the chromatin state undergoes dramatic alternations as the whole genome is duplicated (Annunziato, 2012; Groth, Rocha, et al., 2007). DNA as well as DNA methylation is inherited in a 'semi-conservative' manner (Bell & Labib, 2016; Burgers & Kunkel, 2017). For the passage of replication fork, parental nucleosomes need to be split and evicted from DNA ahead of the replication fork and immediately re-assembled onto the nascent DNA. The transmission of chromatin states during DNA replication depends on the coordination of several processes, including recycling of parental histones, de novo deposition of newly synthesized histones, and nascent nucleosome assembly (Fig. 1).

2.1. Recycling of parental histones

The majority of parental $(H3\text{-}H4)_2$ tetramers do not split during DNA replication and the newly synthesized H3-H4 histones are also deposited in tetramer form, which means parental and newly synthesized $(H3\text{-}H4)_2$ tetramers are assembled into distinct nucleosomes (Fazly et al., 2012; Liu et al., 2012; Su et al., 2012; Xu et al., 2010). In contrast, both parental and newly synthesized H2A-H2B dimers can be assembled into nucleosomes containing parental $(H3\text{-}H4)_2$. It suggests that the recycling of H3-H4 and H2A-H2B occurs in different pathways. Currently, most studies focus on the recycling of H3-H4 as it is more stable on the chromatin and thought to carry more epigenetic information. Using *in vitro* replication system, parental H3-H4 has been shown to recycle to replicating DNA with two different modes: local recycling and dispersal recycling depending on the components of the replisome (Madamba et al., 2017). Consistently, recent studies have revealed parental H3-H4 was transferred to nascent DNA at the replication fork by the coordination of a set of replisome components and histone chaperones to avoid loss of epigenetic information. MCM2, a subunit of the CMG replicative helicase, contains a histone binding domain (HBD) that binds to both histones H3-H4 dimer and tetramer (Foltman et al., 2013; Ishimi et al., 1996, 1998, 2001; Richet et al., 2015). Two studies in yeast and mammalian cells simultaneously showed that both parental and newly synthesized histones have symmetrically distributed on leading strands and lagging strands during DNA replication (Gan et al., 2018; Petryk et al., 2018; Yu, Gan, et al., 2018). Mutation of the HBD domain of MCM2 results in a marked enrichment of parental histones on the leading strand. It indicates that MCM2 directly transfers the disassembled parental H3-H4 to the lagging strand DNA at the replication fork. Importantly, the impaired parental histone transfer by mutated MCM2 results in the increase of epigenetic heterogeneity in draught cells and eventually causes embryonic lethality and tumor progression (Tian et al., 2023; Wen et al., 2023; Wenger et al., 2023). However, MCM2 cannot directly assemble the recycled parental histones into nucleosomes; indicating that it needs to form complex with other histone chaperones for deposition (Groth, Corpet, et al., 2007; Huang et al., 2015; Richet et al., 2015). MCM2 is reported to directly interact with core histone chaperones including ASF1 (Anti-Silencing Factor 1), FACT (FAcilitates Chromatin Transcription) as well as histone variants specific chaperones like HJURP for faithful maintenance of specific chromatin states during DNA replication (Clément et al., 2018; Wang et al., 2023; Zasadzińska et al., 2018). Moreover, recent studies showed that disassembled parental H3-H4 bound MCM2 and was subsequently transferred to lagging strand via Ctf4 (Chromosome Transmission Fidelity 4) and Polα (DNA polymerase alpha) (Gan et al., 2018; Li et al., 2020). The formation of the Mcm2-Ctf4-Polα axis connects two critical events: the recycling of parental histones and the progression of DNA replication fork (Gan et al., 2018). Pol ε,another DNA polymerase, is also reported to play a central role in the transfer of parental histones to nascent DNA. Pol ε is the major leading strand polymerase in eukaryotes, POLE3 and POLE4 subunits of Pol ε interact with histone H3-H4 (Bellelli, Belan, et al., 2018; Burgers &

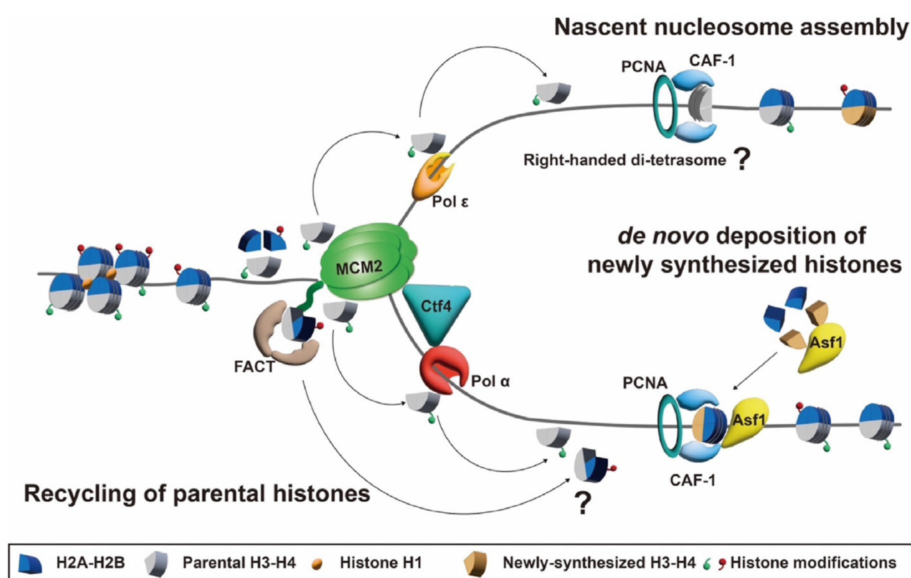

Fig. 1. Parental histone recycling and nascent nucleosome assembly at the replication fork.
During DNA replication, the MCM helicase unwinds unreplicated DNA and promotes the advancement of the replication fork. The disrupted parental histone H3-H4 is bound by histone chaperone FACT in the form of hexamers as well as MCM in the form of tetramer. Parental histone was subsequently transferred to the leading strand and lagging strand with the help of Pol ε, Ctf4, and Pol α. The recycled parental H3-H4 together with newly synthesized H3-H4 escorted by Asf1 are further re-assembled into nucleosomes by downstream histone chaperones like CAF-1 on the replicating DNA. During replication-coupled nucleosome assembly, CAF-1 promotes the formation of a right-handed DNA wrapping H3-H4 tetrasome as a precursor. Subsequently, the joining of H2A-H2B dimers converts the precursor into a mature left-handed nucleosome.

Kunkel, 2017; Foltman et al., 2013; He et al., 2017; Yu, Gan, et al., 2018). In both *Saccharomyces cerevisiae* and mESCs, depletion of POLE3 or POLE4 resulted in a significant increase in the abundance of parental histones on the lagging strand (Wen et al., 2023; Yu, Gan, et al., 2018). It indicates that POLE3 or POLE4 are responsible for the transfer of parental histones to the leading strand. Meanwhile, another study showed that disruption of the POLE3-POLE4 dimerization, which forms a dimer similar to H2A-H2B during replication, leads to loss of the repressive chromatin state during cell divisions (Bellelli, Belan, et al., 2018; He et al., 2017). Interestingly, Pol ε is reported to interact with the human silencing hub (HUSH) complex to facilitate the preferential recycling of H3K9me3-modified parental histones to leading strand DNA on interspersed nuclear element (LINE) retrotransposons (Li et al., 2023). Apart from the function in parental histone transfer, Pol ε was also reported to regulate the assembly of newly synthesized histones (Bellelli et al., 2018a, 2018b). Depletion of POLE3 or POLE4 also causes developmental defects and tumor progression in mammal cells that is similar to the MCM2-2A mutation phenotypes (Tian et al., 2023; Wen et al., 2023). Moreover, depletion of POLE4 impairs replication origin activation and genome stability, which subsequently causes defective lymphocyte maturation in mouse models. The transferring of parental histones to the leading strand and lagging strand takes different pathways centered on Pol ε and MCM2, respectively. Why eukaryotes choose this mechanism may be that two daughter cells could easily achieve consistent inheritance of parental chromatin states through allocation by replisome. Meanwhile, the recycling of parental histones to the leading or lagging strand may be suppressed under different external signaling stimuli, respectively, thus driving the asymmetric fate of daughter cells.

H2A-H2B also carries important epigenetic information, however, there's less research focused on the recycling of H2A-H2B. One reason is that H2A-H2B is more dynamic after incorporation into chromatin and exchanges frequently with other H2A-H2B in the pool or H2A-H2B variants after replication. So, it is technically more challenging to capture the replication-coupled dynamics of H2A-H2B. A recent study using SCAR-seq and ChOR-seq revealed that H2A-H2B is recycled with its modifications, which plays an important role in the restoration of H3-H4 modifications after replication. In addition, H2A-H2B dimers are found to be distributed equally to both daughter strands. This symmetric recycling ensures that both strands receive an equal share of the parental histone H2A-H2B dimers (Flury et al., 2023). However, the detailed molecular mechanism regulating H2A-H2B recycling remains unknown. One possibility is that H2A-H2B is recycled together with H3-H4. FACT consists of two subunits: Spt16 and SSRP1 in mammalian cells which bind to both $(H3\text{-}H4)_2$ tetramers and H2A-H2B dimers (Belotserkovskaya & Reinberg, 2004; Formosa & Winston, 2020; Yang et al., 2016). *In vitro* and *in vivo* experiments have demonstrated that FACT is essential for the advancement of replication forks as well as parental histone recycling (Belotserkovskaya & Reinberg, 2004; Formosa & Winston, 2020). In both yeast and mammalian cells, FACT has been reported to interact with the MCM2-7 complex and they cooperate to facilitate chromatin unwinding during DNA replication (Gambus et al., 2006; Tan et al., 2006). Moreover, recent structural biological discoveries revealed the molecular mechanism by which FACT recognizes and binds nucleosomes as well as its interaction with replisome components (Gan, Yang, Wei, Zhang, & Xu, 2024; Li et al., 2024; Wang et al., 2018). This provides us with the potential function mode of FACT in parental histone recycling. At the replication fork, FACT associated with histone hexamer, consisting of one H2A-H2B dimer and one $(H3\text{-}H4)_2$ tetramer, is observed on both endogenous purified yeast replisome and an *in vitro* assembled system (Gan et al., 2024; Li et al., 2024). One H2A-H2B dimer is evicted from the nucleosome during replication, and the remaining histone hexamer is tethered to the replisome by interaction of the Spt16 MD-CTD domain with the MCM2 HBD domain. This indicates that parental histones might be recycled in the form of a hexamer. Subsequently, the recycled hexamer will be further assembled into a nucleosome on the replicating DNA via the incorporation of one newly synthesized H2A-H2B dimer or the evicted parental H2A-H2B dimer. This conception is consistent with the finding that both parental and newly synthesized H2A-H2B dimers can be assembled into nucleosomes containing parental $(H3\text{-}H4)_2$ (Xu et al., 2010). Moreover, it was found that POLA1 serves as a landing platform for both parental H2A-H2B and H3-H4. A mutation in the histone binding domain of POLA1 results in a dramatic leading-strand biased transfer of parental H3-H4, but a more moderate leading-strand bias for parental H2A-H2B (Flury et al., 2023). This is also probably due to the recycling of one H2A-H2B dimer together with one H3-H4 tetramer as a hexamer, while another H2A-H2B dimer is recycled through alternative pathways. More importantly, our recent single-molecule studies showed that FACT has different kinetic characteristics when disassembling and assembling nucleosomes with different histone variants and modifications (Luo et al., 2023; Wang et al., 2022; Xiao et al., 2020), suggesting that FACT may be an upstream factor that regulates histone variant- and modification-specific epigenetic memory during replication or transcription. Hence, further researches are required to focus on the inheritance of chromatin states predominantly marked by H2A-H2B modifications and variants.

2.2. De novo deposition of newly synthesized histone and nascent nucleosome assembly

During the S phase, as the genomic DNA is duplicated, the recycled parental histones contribute to about half amount of the total histones in daughter strands. Therefore, deposition of the newly synthesized histones on replicating DNA is required to faithfully maintain the nucleosome density and chromatin states in daughter cells.

Asf1 is a conserved H3-H4 histone chaperone that plays an important role in transferring newly synthesized histones H3-H4 to the nascent DNA at the replication fork (Groth, Corpet, et al., 2007; Mousson et al., 2005). Partial depletion of Asf1 in *Drosophila* and mammalian cells severely slows down the S-phase progression (Groth, Corpet, et al., 2007; Schulz & Tyler, 2006). However, Asf1 does not directly assemble nucleosomes on the nascent DNA, instead, it could cooperate with other histone chaperones in depositing the newly synthesized histones (Donham et al., 2011). Structural studies showed that Asf1 binds the C-terminus of histone H3 thus blocking the formation of H3–H4 tetramers (English et al., 2006). To further assemble the H3-H4 into a nucleosome, Asf1 interacts with histone chaperones such as CAF-1 or HIRA through a B-domain-binding pocket and hands off H3-H4 dimers to these histone chaperones for deposition of the newly synthesized histones at the replication fork (De Koning et al., 2007; Feng et al., 2022; Mousson et al., 2007).

CAF-1 (Chromatin assembly factor 1) is the first discovered histone chaperone involving the replication-coupled nucleosome assembly (Hoek & Stillman, 2003; Smith & Stillman, 1989), which is recruited to replication forks through its interaction with PCNA (Moggs et al., 2000; Shibahara & Stillman, 1999; Zhang et al., 2000, 2016). CAF-1 is an evolutionarily conserved heterotrimeric complex that is composed of p150, p60, and p48 in mammalian cells, corresponding to Cac1, Cac2, and Cac3 in yeasts (Liu et al., 2016; Sauer et al., 2017). The atomic resolution structure of the CAF-1-histone H3-H4 complex reveals that once CAF-1 binds to one H3-H4 dimer, the highly negatively charged ED-loop of CAF-1 p150 subunit switches from a disordered to an ordered conformation which tightly binds to histone H3-H4 like a belt (Liu, Yu, Xiong, et al., 2023). *In vitro* supercoiling assay and *in vivo* RelN-Map assay show that the C-terminus of p150 ED-loop is pivotal for the replication-coupled nucleosome assembly function of CAF-1. Mutations in this domain severely impair the nascent nucleosome assembly in mammalian cells and cause transcriptional dysregulation subsequently. Moreover, it has been found that the three subunits of CAF-1 cooperate to bind histone H3-H4 in a very unique mode (Liu, Yu, Xiong, et al., 2023). The p60 subunit blocks the sites where the H3-H4 dimer could further form a tetramer, explaining the inability of CAF-1 to directly bind to the $(H3\text{-}H4)_2$ tetramer. Replicating DNA also plays a role in the

CAF-1-mediated nascent nucleosome assembly, because association with DNA would promote the dimerization of two CAF-1 complexes and two H3–H4 dimers, which is followed by forming H3–H4 tetramer for nucleosome assembly (Quivy et al., 2001). Mutant histones with impaired $(H3\text{-}H4)_2$ tetramerization interactions fail to be released from CAF-1 (Sauer et al., 2017). This indicates that DNA deposition of $(H3\text{-}H4)_2$ tetramers by CAF-1 requires a hierarchical cooperation between DNA binding, histone tetramerization and H3-H4 deposition. Consistently, structural biological study reveals that the addition of 30-bp linker DNA promotes the dimerization of two CAF-1–H3-H4 complexes. Interestingly, adding 147-bp Wisdom 601 DNA could result in an unexpected right-handed $(H3\text{-}H4)_2$ di-tetrasome. The right-handed di-tetrasome is further confirmed by *in vitro* single-molecule magnetic tweezer experiments (Liu, Yu, Xiong, et al., 2023). It was proposed to be a form of nucleosome precursor during DNA replication coupled nucleosome assembly. Future *in vivo* studies are required to better understand the function and biological meaning of this nucleosome precursor during DNA replication. Taken together, these results indicate that the deposition of newly synthesized H3-H4 tetramers by CAF-1 requires the cooperation of DNA-binding activity and dimerization of CAF-1 as well as H3-H4 tetramerization.

3. Epigenetic inheritance following the passage of the replication fork

The passage of replication fork disrupts all nucleosomes in the genome and removes chromatin-binding proteins including transcriptional factors, chromatin modifiers, and chromatin remodelers. To faithfully transmit epigenetic information from parental cells to daughter cells, the recycled parental histones should work together with multiple regulators to fully restore the repressive or active chromatin states at different levels (Bai et al., 2010; Li et al., 2015; Mavrich et al., 2008; Ramachandran & Henikoff, 2016; Segal et al., 2006; Weiner et al., 2010; Whitehouse & Smith, 2013; Yan et al., 2018). Recent studies have highlighted several important events in this process including nucleosome position re-establishment, transcriptional re-start, and histone modifications restoration.

3.1. Re-establishment of nucleosome position and transcriptional restart

The first step in the re-establishment of chromatin state after DNA replication is to reposition the newly assembled nucleosomes. Several studies reveal that nucleosomes are initially randomly positioned in nascent chromatin and later moved to their original position later (Annunziato & Seale, 1982; DePamphilis & Wassarman, 1980; Klempnauer et al., 1980; Stillman, 1986). The time it takes to re-position a nucleosome depends on its chromatin environment before replication (Gutierrez et al., 2019; Serra-Cardona & Zhang, 2018; Stewart-Morgan et al., 2020). Since yeast chromatin is relatively loose, in general, nucleosome positions are generally reestablished more quickly. In yeast cells, nucleosome positions at the promoter region take only a few minutes to re-establish, which is earlier than the post-replication transcriptional restart (Fennessy & Owen-Hughes, 2016; Vasseur et al., 2016; Yadav & Whitehouse, 2016). In contrast to the promoter region, the nucleosome landscape at the gene body region is re-established more slowly. The nucleosome position in transcriptionally active regions re-establishes faster than in transcriptionally silent regions, and depletion of the core subunit of chromatin remodeling complex leads to altered re-establishment kinetics (Vasseur et al., 2016). This clearly suggests the important roles of transcription activities and chromatin remodeling in this process. In *Drosophila*, the regulation of post-replication landscape re-establishment is more complex. At regulatory elements such as promoter and enhancer regions, the characteristic nucleosome-free regions (NFRs) or nucleosome-depleted regions (NDRs) are lost immediately after the passage of the replication fork. Nucleosome positions are then quickly restored to their pre-replication pattern. The re-establishment of the nucleosome landscape requires CAF-1 mediated nucleosome assembly and the incorporation of transcription factors, RNA Polymerase II, and chromatin remodelers, which facilitate changes in chromatin structure and gene transcription (Liu, Yu, Song, et al., 2023; Ramachandran & Henikoff, 2016) (Fig. 2a). This is consistent with observations in human embryonic stem cells, where nascent chromatin is initially inaccessible to transcription factors during DNA replication, and chromatin accessibility is restored shortly afterward in a manner dependent on RNA polymerase incorporation." (Stewart-Morgan et al., 2019). This suggests that transcription plays an active role in the re-establishment of the nucleosome position. Moreover, a recent study using the time-course imaging method revealed the RNA stably retains its position at active gene regions during replication which is mediated by the interaction between RNA Pol II and PCNA at the replication fork (Fenstermaker et al., 2023). Consistently, a study using iPOND and transcriptional inhibitors reveals the binding of RNA Pol II on the newly replicated DNA recruits chromatin remodelers and transcription factors to reshape the nucleosome landscape (Bandau et al., 2024). These results suggest that some compounds of transcription machinery retain their positions around the replication fork to be ready for the re-start of transcription after the passage of the replication fork. Besides, some genes display distinct rates of maturation for each of the two copies. When the transcription direction is the same with replication, the nucleosome position is re-established faster *vice versa* (Vasseur et al., 2016). This mechanism is supposed to avoid collisions between the replication and transcription. Interestingly, DNA replication may also reshape the transcription plasticity and, consequently, cell-fate decisions by affecting the binding event of cell-specific transcription factors (Owens et al., 2019; Stewart-Morgan et al., 2019; Vasseur et al., 2016). Future studies are required to elucidate the interplay between DNA replication and transcription during differentiation, development and diseases including developmental malformations and cancer.

3.2. Restoration of histone modifications and chromatin state maintenance

Histone modifications associated with both transcriptional activation and silencing are supposed to play a central role in epigenetic cell memory (Cavalli & Heard, 2019). Multiple evidences support the idea that the parental histone modification levels are diluted during replication with their position largely unchanged (Escobar et al., 2021). A part of modified parental histones is accurately recycled immediately after DNA replication and re-incorporate in close proximity to the position pre-replication (Gan et al., 2018; Petryk et al., 2018; Reverón-Gómez et al., 2018; Yu, Gan, et al., 2018). These recycled parental histones can function as "seeds" to promote propagation of epigenetic modifications on the neighboring newly synthesized histones through a variety of recruitment mechanisms. A study using pulse & chase mass spectrometry reveals that the kinetics of histone modification restoration post DNA replication is found can be broadly classified into two different modes: 'fast and finite' and 'slow and perpetual' (Alabert et al., 2015). Further study with pulse & chase NGS method-ChOR-seq reveals that restoration kinetics of histone modifications are locus-specific: the same histone modification at different genomic locations has different restoration patterns (Reverón-Gómez et al., 2018). For example, active chromatin mark H3K4me3 restores quickly after replication which is mostly complete before the G2 phase. It has the fastest restoration in regions with CpG density and high transcription levels (Reverón-Gómez et al., 2018). The restoration of H3K27me3 takes about a full cell cycle in HeLa cells and mESCs, and the local enrichment of PRC2 and H1-mediated chromatin compaction largely accelerates the restoration of H3K27me3 (Liu, Yu, Song, et al., 2023; Reverón-Gómez et al., 2018). This suggests the faithful restoration of histone modifications dependent local chromatin environment. Below we highlight detailed molecular mechanisms for histone modification restoration after DNA replication as well as its contribution to the chromatin state maintenance.

Many cis-acting epigenetic mechanisms facilitate the faithful maintenance of the cellular identity across multiple cell divisions. A recent

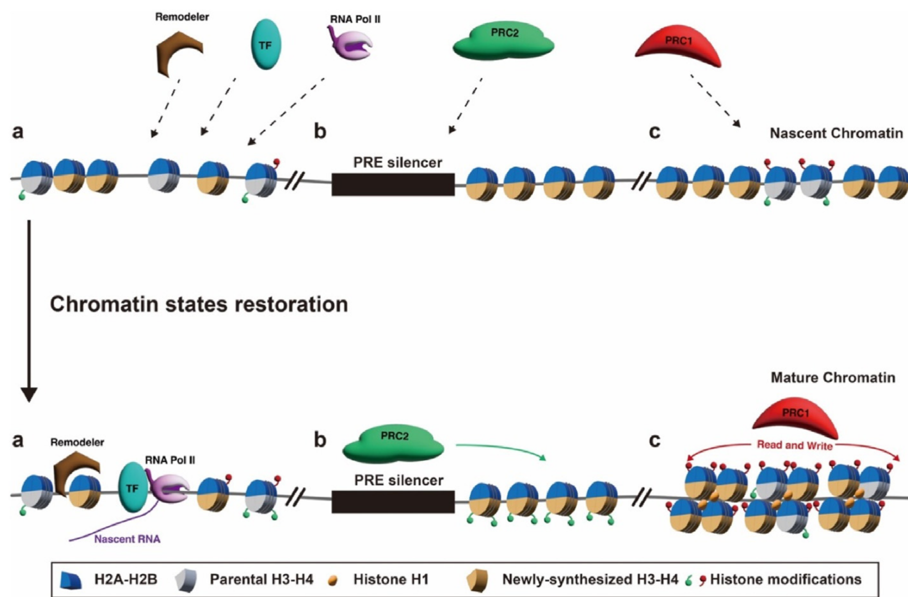

Fig. 2. Chromatin restoration mechanisms after DNA replication.
Shortly after replication, several mechanisms promote the fast restoration of chromatin states in different genomic regions. (a)In active transcription regions, nascent chromatin is largely occupied by newly assembled nucleosomes, which temporarily inhibit transcription. Shortly after, active chromatin states are re-established and transcription re-starts through the cooperation between transcriptional factors, RNAPII, and remodelers. (b) and (c) In the transcriptional repressive regions DNA-sequence dependent and independent recruitment mechanisms promote the restoration of chromatin states after DNA replication. DNA elements like PRE recruit chromatin modifiers PRC2 to restore the occupancy of histone modification H3K27me3 on adjacent nucleosomes and cause subsequent gene silence. Simultaneously, H1 mediated nucleosome-nucleosome pairing mechanism, and RYBP-PRC1 mediated 'Read and Write' mechanism cooperates to facilitate the restoration of histone modification H2AK119ub and to re-establish the silent chromatin state.

study in mESCs using CRISPR-Cas9 editing and BirA mediated proximal labeling reveals parental nucleosomes are preserved locally in repressed chromatin domains; while this pattern is absent in active chromatin domains (Escobar et al., 2019). This suggests that the repressive chromatin state is preserved through more robust mechanisms compared to the active chromatin state's preservation. It is found in many studies that accurate propagation and efficient maintenance of repressive chromatin state through cell cycle follows DNA-sequence dependent and independent recruitment mechanisms (Allshire & Madhani, 2018; Audergon et al., 2015; Coleman & Struhl, 2017; Laprell et al., 2017; Ragunathan et al., 2015; Wang & Moazed, 2017). The first found DNA element required for the maintenance of repressed chromatin is the silencer which mediates the establishment of hypoacetylated domains of silent chromatin in *Saccharomyces cerevisiae* (Cheng & Gartenberg, 2000; Holmes & Broach, 1996). In *Drosophila*, PRE (Polycomb response element) is continuously required for maintaining transcriptional silent state (Fig. 2b) (Ringrose & Paro, 2007). Two studies using ectopic targeting system showed that H3K27me3 levels decreased progressively with cell cycle progression after PRE excision, which further resulted in loss of silencing chromatin state (Busturia et al., 1997; Coleman & Struhl, 2017; Laprell et al., 2017; Sengupta et al., 2004). H3K27me3 declined 10%~12% per cell cycle in *Drosophila* wing discs following PRE excision (Coleman & Struhl, 2017), which further resulted in loss of silencing chromatin state (Busturia et al., 1997; Sengupta et al., 2004). The well-studied DNA-sequence independent mechanism is the positive feedback 'Read and Write' model, which describes a phenomenon that modifications on parental histone recruit/stimulate their writers to propagate the mark to neighbor newly assembled nucleosomes (Fig. 2c) (Margueron & Reinberg, 2010). This is supported by the finding in *Schizosaccharomyces pombe* that Clr4 binds specifically to H3K9me and modifies adjacent nucleosomes, which facilitates the spreading and maintenance of heterochromatin (Zhang et al., 2008). Similarly, a study using *in vitro* methyltransferase assays reveals that mammalian SUV39 recognizes preexisted H3K9me3 through its Chromo domain and subsequently allosteric stimulates its catalytic SET domain, thereby promoting the catalysis of H3K9me3 on neighboring naive nucleosomes (Muller et al., 2016). In *Schizosaccharomyces pombe*, multiple replication components including MCM2 and Mcl1 are required for long-term heterochromatin maintenance and gene silencing (Nathanailidou et al., 2024). Mutating Mcl1 severely impairs the parental histone transferring and results in loss of heterochromatin maintenance. Similarly, mutating the histone histone-binding domain of MCM2 also results in defects in parental histone transferring (Nathanailidou et al., 2024). However, FACT binding to MCM2 facilitates the transferring of a part of parental histones to nascent DNA which results in limited defects in heterochromatin maintenance. This suggests that the 'Read and Write' mechanism mediated by Clr4/Suv39h could compensate for the loss of parental histones during replication but this mechanism also relied on the recycled parental histone 'seeds' to initiate. Besides, the “Read and Write” mechanism is also found to play an important role in the restoration of active chromatin states after DNA replication. In yeast, active chromatin mark H3K4me3 is recognized by the PHD finger of Spp1 (a subunit of COMPASS complex) and subsequently recruits COMPASS complex to the newly replicated chromatin to facilitate the propagation of H3K4me3 on unmodified nucleosomes (Serra-Cardona et al., 2022). In the case of H3K27me3, the EED subunit of Polycomb repressive complex 2 (PRC2) recognizes H3K27me3 and subsequently stabilizes EZH2-catalytic SET domain (Brooun et al., 2016; Jiao & Liu, 2015; Justin et al., 2016; Margueron et al., 2009). Additionally, one PRC2 can bind to an H3K27me3-bearing nucleosome that acts as an allosteric activator to prompt trimethylation of H3K27 on a neighboring nucleosome (Poepsel et al., 2018). This 'Read and Write' positive feedback loop facilitates the local spreading and propagation of H3K27me across cell cycles (Hansen et al., 2008; Margueron & Reinberg, 2010) and especially after DNA replication when modified parental and naive newly synthesized histones are reassembled together on nascent DNA (Lee et al., 2018; Reinberg & Vales, 2018). Recently, we revealed that H2AK119ub also propagates through a positive feedback mechanism, RYBP/YAF subunit of variant Polycomb repressive complex 1 (PRC1) binds H2AK119ub1-bearing nucleosome through its NZF domain and recruits the PRC1 complex to catalyze the ubiquitination of H2A on neighboring nucleosomes (Zhao et al., 2020). Moreover, it was reported that the PRC1 complex can remain stably bound to chromatin and interacts with chromatin remodeler BRG1 to facilitate the proper chromatin assembly during replication (Francis, 2009; Francis et al., 2009; Lengsfeld et al., 2012; Lo et al., 2012; Takano et al., 2022). Accordingly, the RYBP/YAF mediated 'Read and Write' mechanism may function immediately after the passage of the replication fork to secure polycomb silencing on target genes. Besides, H3K27me3 modified by PRC2 also promotes the binding of PRC1 through its chromodomain; this synergy further enhances the spreading of H3K27me3 and H2AK119ub and the propagation of the repressive chromatin state. (Cao et al., 2002; Czermin et al., 2002; Fischle et al., 2003; Kuzmichev et al., 2002; Muller et al., 2002). Consistently, it has been reported that faithful inheritance of chromatin state and stable

transcriptional repression on polycomb target genes requires dynamic crosstalk between H2AK119ub and H3K27me3 during replication. The kinetics of H2AK119ub recycling and restoration are more rapid and transient, as the level of H2AK119ub level undergoes a dramatic decrease during the M phase. Shortly after the passage of the replication fork, recycled H2AK119ub at polycomb genes probably plays two distinct roles at this stage. First, it spreads on the chromatin fiber through a positive feedback loop mediated by RYBP/YAF2 for the restoration of H2AK119ub and gene silencing before transcriptional restart at this locus. Secondly, it promotes the restoration of H3K27me3 via crosstalk between PRC1 and PRC2. H3K27me3 was reported to have a gradual restoration of kinetics and the genome-wide H3K27me3 level steadily increases across the M phase. Therefore, on common target genes of H2AK119ub and H3K27me3, the transcriptional memory was preserved by the short-term repression by H2AK119ub and the long-term repression by H3K27me3 together. Interestingly, other H2A-H2B modifications and variants are also reported to interact with H3-H4 modifications. Due to the dynamic feature of the H2A-H2B dimer, further studies are required to reveal whether they play a similar role in the early stage of the S phase. It will be interesting to see that the recycled H2A-H2B acts like a 'pioneer' to transmit the short-term epigenetic information which challenges the current understanding that most modifications on H2A-H2B might not be heritable. Besides, non-coding RNAs, RNA interference, and DNA methylation also contribute to the establishment and maintenance of a repressive chromatin state (Allshire & Madhani, 2018; Almeida et al., 2017; Yu, Wang, & Moazed, 2018). Further studies are required to reveal their dynamic roles during DNA replication.

Cumulative studies have shown that long-term epigenetic inheritance mainly occurs at broad heterochromatin domains (Kaufman & Rando, 2010; Rando & Chang, 2009), suggesting that higher-order chromatin structure plays a pivotal role in the transmission of chromatin states during the cell cycle. The organization of high-order chromatin basically requires the incorporation of histone H1 to fold nucleosome arrays (Li & Reinberg, 2011). Cryo-EM studies revealed that linker histone H1 compacts nucleosome arrays into double helix conformation twisted by tetranucleosomal units *in vitro*, which is stabilized by the pseudo-two-fold symmetric nucleosome-pairing interactions between the H2B-helix α1/αC and the H2A-helix α2 of alternative nucleosomes and the interactions between the H4 N-terminus and the H2A-H2B acidic patch of a neighboring nucleosome (Song et al., 2014). Interestingly, disruption of the nucleosomal stacks by H2B αC-helix mutations or N-terminal truncated H4 compromised the spreading of H2AK119ub on chromatin fibers, suggesting that conformational changes in chromatin, such as changes in the distance of neighboring nucleosome or the twist of chromatin fiber, might actively contributing to promoting the propagation and inheritance of histone modifications. An early study using *in vitro* methyltransferase assays revealed that dinucleosomes or nucleosome arrays with H1 are optimal substrates of PRC2 complexes, which in turn promotes the spreading of H3K27me3 on nucleosome arrays (Martin et al., 2006). In addition, dense oligonucleosomes and chromatin compaction mediated by Mg2+ or H1 activate PRC2 (Polycomb repressive complex 2) through allosteric activation by neighboring nucleosomes (Yuan et al., 2012). Consistently, our recent study using ChOR-seq also revealed that chromatin structure disruption by *H1c/d/e*-triple knockout in mESCs resulted in a dramatic slowdown in the restoration kinetics of H3K27me3 post DNA replication. Interestingly, induced degradation of H1 in a short period before affecting the total H3K27me3 level causes a more significant decrease in the H3K27me3 restoration. This suggests the central role of H1-mediated chromatin compaction in regulating the H3K27me3 restoration. *In vitro* biochemical experiments showed that the H1-mediated nucleosome-nucleosome pairing facilitated the spreading of H3K27me3 on chromatin fibers. The role of H1-mediated chromatin compaction in regulating histone restoration relies on this propagation mechanism to keep functioning during chromatin maturation after replication. Moreover, the accumulative decrease in H3K27me3 restoration speed across multiple cell cycles finally resulted in an obvious decrease in global H3K27me3 and reduced local chromatin compaction (Fan et al., 2005). Interestingly, we revealed that H1-dependent chromatin compaction promotes RYBP/YAF2 -PRC1-mediated long-distance propagation of H2AK119ub1 via a positive feedback loop, and both histone H1 and RYBP/YAF2-PRC1 are required for the stable transmission of H2AK119ub1 during cell division at heterochromatin regions. Disruption of H1-dependent chromatin compaction resulted in a dramatic defect in H2AK119ub1 maintenance (Zhao et al., 2020). Further studies are required to reveal the role of chromatin structure in regulating the recycling and restoration of H2AK119ub as H2AK119ub was recently shown to be upstream to H3K27me3 during DNA replication. In addition to local chromatin compaction, spatially long-distance interactions also play an important role in the propagation of repressive chromatin states during cell cycle. A recent study using *in-silico* modeling built on prior experimental findings revealed that higher-order chromatin structure facilitates the stabilization of epigenetic memory during cell cycles (Owen et al., 2023). This stabilization is contingent upon the spatial organization of modified nucleosomes and the propagation ability of 'Read and Write' enzymes. This model is supported by our recent findings that H1-mediated nucleosome-nucleosome interactions, along with the concerted action of 'Read and Writer' enzymes, are essential for the maintenance of repressive chromatin states throughout cell cycles (Zhao et al., 2020; Liu et al., 2023, 2023b). In addition, previous 3D genome studies have revealed that polycomb targets form a cluster of highly enriched H3K27me3 regions in mESCs (Denholtz et al., 2013; Schoenfelder et al., 2015; Vieux-Rochas et al., 2015). These H3K27me3 nucleation sites spatially interact in the mESCs nucleus, and these long-range contacts facilitate the spreading of H3K27me3 to distal chromatin regions (Oksuz et al., 2018). Moreover, repressive chromatin has a less frequent histone turnover rate and more conserved spatial localization which may promote epigenetic inheritance (Aygun et al., 2013; Iglesias et al., 2020; Zentner & Henikoff, 2013). This is supported by the observation in *Schizosaccharomyces pombe* that nuclear rim protein Amo1 together with FACT tethers heterochromatin to the nuclear periphery and prevents histone turnover to retain parental histones locally, which facilitates the inheritance of the repressive chromatin state (Holla et al., 2020). These findings collectively suggest that a network of DNA sequence elements, 'Read and Write' positive feedback loops and higher order chromatin structure facilitate the restoration of chromatin states and faithful epigenetic inheritance after DNA replication.

4. Perspective

Proper inheritance of chromatin states at the replication fork is key to faithful passage of epigenetic information across multiple cell divisions. With the discovery of detailed mechanisms of parental histone recycling, replication-coupled nucleosome assembly, and chromatin maturation in the last decade, central mechanisms and regulators in this process have been identified. Despite these great advances in our knowledge, many critical questions remain open in this field. Firstly, in the study of the regulatory role of higher-order chromatin structure in replication-coupled nucleosome assembly and epigenetic state inheritance, chromatin structure is not static but changes dynamically with the cell cycle progression. This derives many detailed questions. How is the functional higher-order chromatin structure before replication fork inherited? When and how is functional spatial chromatin organization re-established post-DNA replication, particularly at loci with promoter-promoter and promoter-enhancer interactions? What epigenetic factors participate in the regulation of this progress? Secondly, the chromatin states are far more complicated than we discussed in this review, which is generally divided into 'active' and 'repressive' states. Locus-specific DNA methylation, histone modification and variants occupancy, transcription factors binding, chromatin remodelers, ncRNA binding, etc. together coordinate to shape the functional chromatin states, especially in important regulatory gene regions. Future experiments should address

the temporal and spatial dynamic inheritance of these chromatin factors during DNA replication and how these regulatory networks re-establish post DNA replication. Thirdly, current studies focused on the fundamental and general mechanisms, but little is known as yet about how these mechanisms are fine-tuned during important biological processes such as differentiation, development, regeneration, and immune response. During these biological processes, intracellular and intercellular signals stimulate the stem cell or immune cell to duplicate or differentiate. Thus, the replication-coupled inheritance mechanisms play a determinant role in the cell identity decision. Future work focused on the biological process-specific chromatin inheritance mechanisms will provide us with new insights into understanding health-related issues such as aging and diseases as well as providing novel targets to interfere with these processes.

With the development of new technologies, including improving chromatin-based biorthogonal labeling techniques during replication, highly efficient genome editing techniques, novel single-molecule and super-resolution imaging methods, spatial epigenome-transcriptome co-profiling methods, we expect to gain more mechanistic insights into the dynamic and structural change of chromatin during DNA replication and further map the regulatory network of chromatin state inheritance in important biological processes in the coming years.

CRediT authorship contribution statement

Aoqun Song: Writing – original draft. **Yunting Wang:** Writing – original draft. **Cuifang Liu:** Writing – review & editing. **Juan Yu:** Writing – review & editing. **Zixu Zhang:** Writing – review & editing. **Liting Lan:** Writing – review & editing. **Haiyan Lin:** Writing – review & editing. **Jicheng Zhao:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Guohong Li:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors declare no conflicts of interests with this manuscript.

Acknowledgment

We are grateful to all members of Guohong Li lab for their theoretical assistance and technical support in this manuscript. This work was supported by grants from the National Natural Science Foundation of China (31991161 and 32230020 to G.L.), the Ministry of Science and Technology of China (2023YFA0913402 to G.L. and 2019YFA0508903 to J.Z.), the National Natural Science Foundation of China (32270614 and 32070604 to J.Z., 32100470 to C.L., 32370645 to J.Y., 32270581 to H.L.), the Beijing Municipal Science and Technology to G.L. (Z221100007022001), the Fundamental Research Funds for the Central Universities to G.L. (2042022dx0003), and the Basic Research Program of the Chinese Academy of Sciences Based on Major Scientific Infrastructures to G.L. (JZHKYPT-2021- 05). This paper has been supported by the New Cornerstone Science Foundation.

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