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Mechanisms of chromatin-based epigenetic inheritance

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Multi-cellular organisms such as humans contain hundreds of cell types that share the same genetic information (DNA sequences), and yet have different cellular traits and functions. While how genetic information is passed through generations has been extensively characterized, it remains largely obscure how epigenetic information encoded by chromatin regulates the passage of certain traits, gene expression states and cell identity during mitotic cell divisions, and even through meiosis. In this review, we will summarize the recent advances on molecular mechanisms of epigenetic inheritance, discuss the potential impacts of epigenetic inheritance during normal development and in some disease conditions, and outline future research directions for this challenging, but exciting field.

epigenetic inheritance, histone modification, DNA methylation, histone deposition, DNA replication

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Introduction

Epigenetics was coined by Waddington in 1942 as a framework for the generation of distinct phenotypes in multi-cellular organisms (Waddington, 1942). At the time, DNA was not discovered as the carrier of genetic information that governs the transmission of genetic traits from generation to generation. Since then, it has been increasingly clear that epigenetic regulation plays a critical role in the development of multicellular organisms including human, and mis-regulations of the epigenetic network are the drivers for many forms of diseases including cancer and aging (Margueron and Reinberg, 2010; Benayoun et al., 2015; Allis and Jenuwein, 2016; Jones et al., 2016). In this review, we will focus on discussing the molecular mechanisms underlying how epigenetic information is inherited into daughter cells during mitotic cell divisions. While we will mention several examples on the trans-generational epigenetic inheritance, we will concentrate our discussion on epigenetic inheritance during mitosis, and refer the readers to other reviews discussing the mechanisms and the impacts of trans-generational epigenetic inheritance (Heard and Martienssen, 2014; Horsthemke, 2018).

In early days of epigenetic research, scientists described

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and studied biological phenomena that cannot be explained by genetic information alone. These examples include position effect variegation observed in *Drosophila*, X chromosome inactivation in female mammals, genome imprinting in mammals, and para-mutations observed in plants. Position effect variegation is a phenomenon in which the white gene in *Drosophila* eye is expressed in some cells but silenced in others when the white gene translocates closer to heterochromatin region, a highly condensed chromatin domain that is transcriptionally silent (Tartof et al., 1984). That the expression of a gene was based on its location on the chromosome, but not the gene itself, was also observed in budding yeast when a gene was inserted closer to telomeres (telomere position effects) (Gottschling et al., 1990). X-chromosome inactivation in female mammals is a mechanism whereby one of two X-chromosomes is inactivated in female mammals during early embryogenesis to balance the expression of genes on X-chromosomes between male and female. Moreover, once silenced, the inactivated X-chromosome remains silent during subsequent cell divisions (Plath et al., 2002). Genome imprinting is a phenomenon in which the maternal or paternal allele of a gene is expressed, while the other allele is silenced (Ferguson-Smith and Bourc'his, 2018). These examples remain the best to illustrate the modern definition of epigenetics, heritable changes in gene expression/phenotypes without alterations at the underlying DNA sequences (Allis et al., 2007; Margueron and Reinberg, 2010). While not all inheritable epigenetic information is encoded by the chromatin, such as prions, in this review, we will focus on discussion of inheritance of epigenetic information encoded by chromatin in eukaryotes.

In eukaryotic cells, the genetic material forms a highly ordered structure, chromatin, consisting of proteins, DNA and RNA. The basic repeat unit of chromatin is the nucleosome, consisting of 147 bp of DNA wrapped around a histone octamer composed of one H3-H4 tetramer and two H2A-H2B dimers (Zhou et al., 2019; Talbert and Henikoff, 2021). Chromatin is further organized into distinct domains such as heterochromatin and euchromatin, which traditionally represent chromatin regions with inactive and active gene transcription, respectively. For in-depth discussion, please see recent reviews on insights of three-dimensional chromatin structures (Dekker and Mirny, 2016; Yu and Ren, 2017; Li et al., 2020a). Furthermore, heterochromatin and euchromatin are marked by different posttranslational modifications on histones (Figure 1). For instance, di- and tri-methylation of histone H3 lysine 9 (H3K9me2/me3) mark constitutive heterochromatic regions, such as repetitive DNA sequences including endogenous retroviral elements (ERVs), pericentric heterochromatin regions and telomeric heterochromatin (Grewal and Moazed, 2003). On the other hand, tri-methylation of histone H3 lysine 27 (H3K27me3) plays an important role in the repression of gene transcription during development (Margueron and Reinberg, 2011). Besides these repressive marks, other histone modifications are associated with active gene transcription. Tri-methylation of H3 lysine 4 (H3K4me3) is highly enriched at promoters of actively transcribed genes (Shilatifard, 2012), whereas H3K36me3 marks the gene bodies of actively transcribed genes (Wagner and Carpenter, 2012). In addition to histone modifications, histone variants, a group of proteins that adopt similar fold as core histones, reside in specific chromatin regions and are also important for the establishment and maintenance of chromatin states (Loyola and Almouzni, 2007; Talbert and Henikoff, 2010). For instance, histone H3 variant CenH3 proteins occupy centromeric heterochromatin regions and are critical for the establishment of a functional kinetochore for chromosome segregation during mitosis. Histone variant H3.3, which differs from canonical H3.1/H3.2 by 4 or 5 amino acids, marks actively transcribed regions, whereas canonical H3.1/H3.2 are enriched at heterochromatin. Moreover, DNA cytosine can be methylated

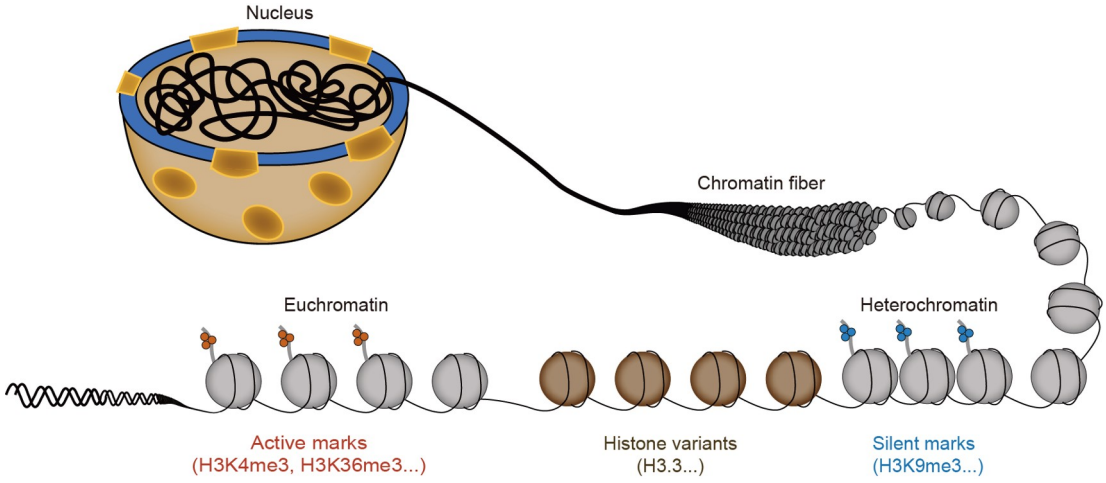

Figure 1 A cartoon depicts representative chromatin states.

(5mC) or hydroxymethylated (5hmC), which are distributed on chromatin differently. At constitutive heterochromatin regions, 5mC co-localizes with H3K9me2/me3 (see detailed discussion below). In contrast, 5hmC in general is found at promoters and enhancers of actively transcribed genes. Finally, non-coding RNAs also play a role in forming distinct chromatin states (Zaratiegui et al., 2007). In summary, chromatin is demarcated by histone modifications, histone variants, DNA methylation and non-coding RNA (not discussed in this review). Together, they play an important role in the establishment and maintenance of chromatin structures, gene expression and cell identity.

During DNA replication, chromatin structures are transiently disassembled to allow DNA replication machinery to access replicating DNA. Following DNA replication, distinct chromatin states, marked by different histone modifications, histone variants, DNA methylation and non-coding RNA must be restored to maintain chromatin structures and gene expression states (Moazed, 2011; MacAlpine and Almouzni, 2013; Serra-Cardona and Zhang, 2017). How distinct chromatin states are inherited following DNA replication lies in the heart of epigenetics. In this review, we will first discuss how nucleosomes, the basic repeat units of chromatin, are assembled following DNA replication, and outline the general principles in the passage of histone modifications into daughter cells. As an example, we will discuss in depth on how H3K9 methylation in *S. pombe* is inherited during mitotic cell division. Furthermore, we will discuss how DNA methylation is inherited, and highlight the potential interplay between DNA methylation and histone modifications to maintain chromatin states. Finally, we will discuss the potential impact of dysregulation of epigenetic inheritance in development and human diseases and outline future research directions for this challenging, but exciting field.

DNA replication-coupled nucleosome assembly

A brief overview of DNA replication in eukaryotic cells

During S phase of the cell cycle, DNA sequence must be faithfully replicated to maintain genome integrity. DNA replication initiates stochastically from DNA replication origins (MacAlpine, 2021). While replication origins are well-defined and contain consensus sequence motifs in *Saccharomyces cerevisiae*, DNA replication origins in higher eukaryotic cells are specified and influenced by local chromatin structures (Hu et al., 2020; Long et al., 2020). The initial step in the initiation of DNA replication is the assembly of pre-replication complex (pre-RC) at a replication origin. During this process, a group of proteins are orderly assembled into a large complex at G1 phase at replication origins (Bell and Dutta, 2002; Burgers and Kunkel, 2017). First, origin recognition complex (ORC), which is composed of six subunits (Orc1–6), recognizes replication origins (Bell and Stillman, 1992), and together with CDC6 and CDC10-dependent transcript 1 (CDT1), loads the hexameric mini-chromosome maintenance (MCM) complex, consisting of MCM2–7, at replication origins to form the pre-RC complex (Donovan et al., 1997; Tanaka et al., 1997). The loaded MCM complexes at this stage are head-to-head inactive double hexamers and encircle double-stranded (ds) DNA. Phosphorylation of the MCM complex by DDK (DBF4-dependent kinase) and CDKs and subsequent binding of CDC45 and the DNA replication complex GINS (go-ichi-ni-san) lead to formation of two active replicative helicases, the CMG helicase (Cdc45-MCM-GINS) (Ilves et al., 2010). The CMG complex unwinds dsDNA into ssDNA, which is coated with ssDNA binding protein, replication protein A (RPA). Two short RNA-DNA primers are then synthesized by the primase-DNA polymerase alpha (Polα) complex, which are used by DNA polymerase epsilon (Polε) to synthesize the leading strands continuously and DNA polymerase delta (Polδ) to synthesize the lagging strands as Okazaki fragments. Finally, Ctf4 (AND1 in mammalian cells) connects the CMG helicase with Polα primase, which likely coordinates leading and lagging DNA synthesis as well as nucleosome assembly of parental histones (See Discussion below). Together, the multi-component protein machinery, namely the replisome, replicates DNA in a highly regulated manner.

An overview of DNA replication-coupled nucleosome assembly

In general, nucleosomes limit the accessibility of protein machinery involved in various DNA transactions such as DNA replication, repair and gene transcription to the nucleosomal DNA. Therefore, during DNA replication, 1-2 nucleosomes ahead of DNA replication forks are temporarily disassembled to allow the replisome to access DNA. Following the passage of DNA replication forks, replicated DNA is reassembled into nucleosomes using both parental histones and newly synthesized histones in a process tightly coupled to on-going DNA replication (DNA replication-coupled nucleosome assembly) (McKnight and Miller, 1977; Stillman, 1986; Li et al., 2013) (Figure 2). Moreover, parental $(H3.1\text{-}H4)_2$ tetramers remain intact and generally do not split during DNA replication (Xu et al., 2010). Meanwhile, newly synthesized H3.1-H4 are deposited onto replicating DNA in tetramer forms mediated by histone chaperones (Fazly et al., 2012; Liu et al., 2012b; Su et al., 2012). Therefore, parental and newly synthesized $(H3.1\text{-}H4)_2$ tetramers form distinct nucleosomes following DNA replication. On the contrary, newly synthesized H2A-H2B could be found in nucleosomes containing parental H3-H4

tetramers in one cell cycle, consistent with the idea that nucleosomal H2A-H2B can exchange relatively freely with parental H2A-H2B following DNA replication. Furthermore, deposition of H3-H4 tetramers is the rate-limiting step of nucleosome formation (Smith and Stillman, 1991). Therefore, we will focus on the discussion of replication-coupled nucleosome assembly into three parts, dis-assembly of preexisting nucleosomes (or parental nucleosomes) located ahead of the replication fork, recycling of parental histone H3-H4 tetramers, and deposition of newly synthesized H3-H4 tetramers to form nucleosomes *de novo*.

Disassembly of parental nucleosomes

Previous studies reveal that approximately 300 bp of naked DNA resides ahead of the replication forks, suggesting that 1-2 nucleosomes ahead of DNA replication forks are temporarily disrupted (Lucchini et al., 2001). In *Xenopus* egg extracts, using single-molecule imaging, it was reported that nucleosome ahead of the replication fork is evicted and parental histones are recycled (Gruszka et al., 2020). Together, these studies support the idea that nucleosomes ahead of DNA replication forks are disassembled temporarily.

Several factors are likely involved in the disassembly of nucleosomes ahead of DNA replication forks. First, ATP-dependent chromatin remodeling complexes, which utilize the energy of ATP hydrolysis to alter the position of nucleosomes along the DNA and to evict nucleosomal histones, are likely involved in this process. Supporting this idea, several chromatin remodeling complexes including INO80, SWR1, ISW1 and ISW2 in budding yeast and their mammalian counterparts also participate in the DNA replication process (Papamichos-Chronakis and Peterson, 2008; Vincent et al., 2008; Morrison and Shen, 2009; Kurat et al., 2017). However, to what extent that these chromatin remodeling complexes remodel parental nucleosomes ahead of DNA replication forks remains elusive. Second, the FACT (facilitates chromatin transactions) complex has been implicated in remodeling nucleosomes ahead of DNA replication forks. FACT, consisting of two subunits, Spt16 and Pob3 (SSRP1 in mammals), is a histone chaperone that binds to both H3-H4 tetramers and H2A-H2B dimers (Belotserkovskaya and Reinberg, 2004; Formosa and Winston, 2020). It has been shown that FACT is essential for transcription on chromatin template *in vitro* proposedly through removing H2A-H2B from nucleosomes (LeRoy et al., 1998; Orphanides et al., 1998). Recent studies using purified proteins in reconstituted DNA replication system indicate that FACT is also essential for DNA replication through chromatin template (Kurat et al., 2017). Thus, FACT plays an important role in both DNA replication and gene transcription through chromatin. *In vitro*, FACT can alter the contacts between histones and DNA without ATP hydrolysis. However, FACT itself could not disassemble nucleosomes *in vitro* (Chen et al., 2018; Wang et al., 2018b). Based on the Cryo-EM structures, FACT recognizes partially unwrapped nucleosome structures (Liu et al., 2020). In cells, FACT co-purifies with MCM2-7 complex in both yeast and mammalian cells. FACT can also promote DNA unwinding by MCMs *in vitro* (Gambus et al., 2006; Tan et al., 2006). Together, these studies suggest that after nucleosome disassembly, FACT may work with MCM helicase complex to facilitate nucleosome reassembly during DNA replication (Figure 2). However, whether and how FACT functions in parental nucleosome disassembly and subsequent transfer of parental histones onto replicated DNA remain unclear. Finally, Asf1, another histone chaperone proposed to be involved in parental nucleosome disassembly, is best known for its role in shuttling newly synthesized H3-H4 in the process of *de novo* nucleosome assembly. It has been shown that Asf1 co-purifies with MCM2–7 complex in mammalian cells, and this interaction is bridged by histone H3-H4 in the nucleus (Groth et al., 2007). A mutation on Asf1-V94R, which disrupts Asf1 binding to H3-H4, also compromise the Asf1-MCM interactions. Structure analysis of the Asf1-H3-H4-MCM2 complex indicates that MCM2 N-terminus can bind to the H3-H4 tetramer and hijack the H3 interface involved in tetramer formation (Clément and Almouzni, 2015; Huang et al., 2015). In cells, it has been shown that histone chaperone Asf1 can facilitate nucleosome disassembly at promoter region or gene body during transcription (Adkins et al., 2004; Adkins and Tyler, 2004; Gao et al., 2018). However, Asf1 cannot disassemble nucleosomes *in vitro*, indicating that other factors collaborate with Asf1 to accomplish parental histone eviction *in vivo* (Donham et al., 2011). Together, these studies suggest that multiple factors including chromatin remodeling complexes and histone chaperones are likely involved in the disassembly of nucleosomes ahead of DNA replication forks. However, to what extent these factors function in nucleosome disassembly and subsequent parental histone transfer remains to be determined.

Parental histone transfer at the replication forks

Once parental nucleosomes ahead of replication forks are disassembled, parental histones with modifications must be transferred onto replicating DNA strands for the formation of nucleosomes. This parental histone transfer and/or recycling process is critical for the inheritance of histone modifications, but remains elusive for over 4 decades. For instance, based on metabolic labeling of DNA and proteins during S phase, it was proposed that parental histones are randomly and equally distributed onto replicated DNA strands (Seale, 1976). Recent studies indicate that parental H3-H4 tetramers likely remember their position along the DNA. These studies are made possible with the development of novel techniques.

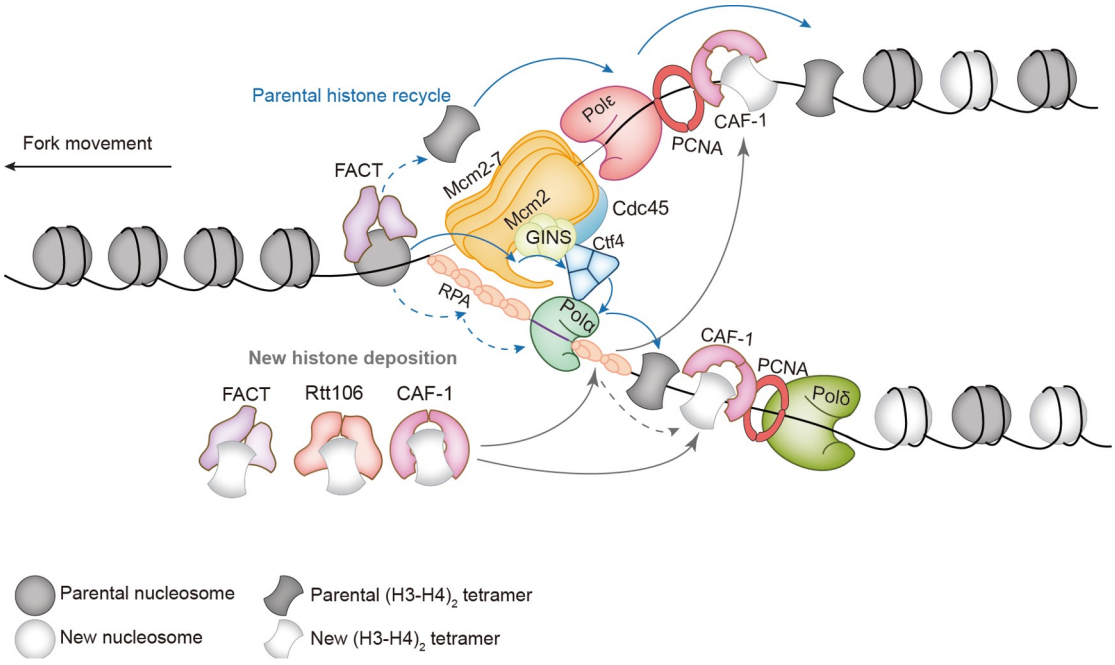

Figure 2 DNA replication coupled nucleosome assembly pathways with key factors involved in nucleosome assembly indicated.

For instance, by monitoring parental H3-H4 on a plasmid in two different *in vitro* DNA replication systems, it has been shown that parental H3-H4 are transferred locally in the *Xenopus* DNA replication system, but are dispersed in SV40 DNA replication system (Madamba et al., 2017). The major distinction between these two systems is that different helicases are used in the DNA replication. In *Xenopus* extract, CMG is the replicative helicase, whereas large T antigen is the replicative helicase in the SV40 DNA replication system. More recently, two studies show that parental nucleosomes form positional memory following DNA replication (Escobar et al., 2019; Schlissel and Rine, 2019). Both studies started with labeling parental nucleosomes at a particular locus covalently with biotin, and then tracked the fate of labeled nucleosomes through DNA replication. In budding yeast, it has been shown that labeled histone H3 can remember its positions along the DNA following replication and gene transcription (Schlissel and Rine, 2019). In mouse embryonic stem (ES) cells, by monitoring parental nucleosomal H3.1 that is enriched at silent chromatin regions, it has been shown that parental H3.1 is transferred locally at repressive regions, but is dispersed at actively transcribed regions (Escobar et al., 2019). Of note, H3.3, but not H3.1, is enriched at actively transcribed regions (Loyola and Almouzni, 2007; Talbert and Henikoff, 2010). Therefore, it would be interesting to determine whether parental H3.3 is also transferred locally or dispersed at actively transcribed regions.

Recent studies have discovered specific protein factors involved in the transfer of parental H3-H4 onto replicating DNA (Figure 2). First, it has been shown in both yeast and mouse ES cells, mutations at the histone binding motif of MCM2, a subunit of the CMG helicase, result in defects in the transfer of parental H3-H4 to lagging strands of DNA replication forks (Gan et al., 2018; Petryk et al., 2018). Early studies indicate that human MCM complex binds to H3 and H4 in HeLa cell extracts, and the N-terminus of mouse MCM2 is required for the histone binding activity (Ishimi et al., 1998; Ishimi et al., 2001). Similarly, the N-terminal histone binding motif (HBM) of yeast Mcm2 was reported to interact with all four histones released from chromatin (Foltman et al., 2013). Interestingly, mouse MCM2 can bind to H3-H4 and assemble a nucleosome-like structure *in vitro*, supporting the idea that MCM2 histone binding domain also possesses histone chaperone activity. Using the eSPAN (enrichment and sequencing of protein-associated nascent DNA) that measures the relative amount of parental and newly synthesized histones at the leading and lagging strands of DNA replication forks, it has been shown that parental H3 marked with H3K4me3 are transferred almost equally to leading and lagging strands, with a slight preference for lagging strands (Yu et al., 2018a). In contrast, new histones marked by H3K56ac (acetylation on H3 lysine 56) showed an opposite pattern. In cells with *mcm2-3A* mutation that disrupts the interaction between Mcm2 and H3-H4, parental H3K4me3 are enriched at leading strands due to defects in the transfer of parental histones to lagging strands (Gan et al., 2018). Similarly, using SCAR-seq (sister chromatids after replication by DNA sequencing) in mouse ES cells with mutations disrupting MCM2 binding to histones, marks on

parental histone show asymmetric distribution (Petryk et al., 2018). These results show that the histone binding ability of MCM2 is critical for parental histone transfer to lagging strands of DNA replication forks.

The CMG helicase interacts with leading strand polymerase Polε and travels along with leading strand template (Fu et al., 2011; Burgers and Kunkel, 2017). How does MCM2, traveling along the leading strands, facilitates the transfer of parental histones to the lagging strands of DNA replication forks? To answer this question, it should be noted that the CMG helicase interacts with Ctf4, which forms a trimer that also interacts with Pol1, the catalytic subunit of Polα primase enriched at lagging strands (Simon et al., 2014). Studies from budding yeast show that mutations at Ctf4 that cannot bridge the CMG-Pol1 interaction or Pol1 mutants that cannot bind to Ctf4 display similar defects in parental histone transfer to lagging strands (Gan et al., 2018). Finally, like Mcm2, Pol1 also contains a conserved histone binding motif (Evrin et al., 2018). Both yeast and mouse Pol1 bind to H3-H4 preferentially over H2A-H2B. Mutations at the histone binding motif of Pol1 also result in defects in parental histone transfer in a manner similar to Mcm2 mutant defective in histone binding (Li et al., 2020b). Together, these studies indicate that Mcm2-Ctf4-Polα axis regulates the transfer of parental histone H3-H4 to lagging strands of DNA replication forks.

In budding yeast and mouse ES cells, using eSPAN analysis, it has been shown that deletion of Dpb3 (POLE4 in mammals) or Dpb4 (POLE3 in mammals) leads to the dramatic reduction of the transfer of parental histones to leading strands of DNA replication forks (Yu et al., 2018a). Dpb3 and Dpb4 are two subunits of leading strand DNA polymerase, Polε. However, Dpb3 and Dpb4 are not required for enzymatic activity of Polε. Dpb3 and Dpb4 in fission yeast form a dimer with the structure similar to H2A-H2B (He et al., 2017). Moreover, Dpb3-Dpb4 co-purify with all four core histones (Tackett et al., 2005) and interact with H3-H4 preferentially over H2A-H2B *in vitro* (Yu et al., 2018a). Similarly, POLE3-POLE4 formed a stable dimer and could bind to histone H3-H4 directly but not H2A-H2B (Bellelli et al., 2018). Together, these studies indicate that Dpb3 and Dpb4 serve as histone chaperones to promote the transfer of parental histones to leading strands of DNA replication forks.

Budding yeast cells with *mcm2-3A* mutation showed mild defects in the loss of transcriptional silencing at heterochromatin loci. Similar effects were also observed for cells lacking Dpb3 and Dpb4 in both budding and fission yeast (He et al., 2017; Yu et al., 2018a). Moreover, *mcm2-3A dpb3* double mutant cells show defects in memory of nucleosome positions following DNA replication (Schlissel and Rine, 2019). In mouse ES cells, the MCM2 and Polα mutants with impaired parental histone transfer show defects in the repression of ERVs (Li et al., 2020b). Together, these studies indicate that the precise transfer of parental H3-H4 to replicating DNA strands is important to maintain heterochromatin states. Of note, both yeast and mouse ES cells lacking these factors involved in parental histone transfer have largely normal growth, suggesting that additional factors participate in the transfer of parental histones.

Deposition of newly synthesized histone H3-H4

After DNA duplication, parental histones contribute to only half of the total histones required for the assembly of replicating DNA into nucleosomes. Therefore, newly synthesized histones are needed to complete the nucleosome assembly of replicated DNA. Compared with the transfer of parental histones, *de novo* deposition of new H3-H4 is relatively well studied (Serra-Cardona and Zhang, 2017). As detailed below, *de novo* deposition of new H3-H4 requires a group of histone chaperones that mediate histone folding, import and deposition onto replicating DNA. Moreover, modifications on newly synthesized H3-H4 also regulate the interactions between histones and histone chaperones. Finally, these histone chaperones interact with components of replisomes to facilitate the deposition of new H3-H4 onto replicating DNA strands (Figure 2).

Histone chaperones form a coordination network for deposition of new H3-H4

Histone chaperones are essential for *de novo* histone deposition. These histone chaperones form a coordination network for the deposition of newly synthesized H3-H4, which first form a heterodimer. With the aid of other protein chaperones involved in protein folding, new H3-H4 form a complex with histone chaperone Asf1, which does not show nucleosome assembly activity *in vitro*, indicating that Asf1 may not participate in the assembly event directly (Tyler et al., 1999; English et al., 2005; English et al., 2006). Consistent with this observation, the structure of Asf1-H3-H4 complex reveals that Asf1 binds to the H3-H4 dimer through the H3 interface involved in the formation of H3-H4 tetramers, and thus Asf1 blocks the H3-H4 tetramer formation (English et al., 2006). Therefore, once associated with Asf1, H3-H4 must be transferred to downstream chaperones including chromatin assembly factor 1 (CAF-1) for deposition onto replicating DNA.

CAF-1 was the first histone chaperone discovered involved in replication coupled nucleosome assembly (Stillman, 1986; Verreault et al., 1996; Kaufman et al., 1997). CAF-1 consists of three subunits, Cac1, Cac2 and Cac3 in yeast, corresponding to p150, p60 and p48 in mammalian cells. One CAF-1 molecule binds to one H3-H4 dimer and the dimerization of two CAF-1 complexes triggers the formation of a H3-H4 tetramer (Liu et al., 2016; Mattiroli et al.,

2017). Asf1 binds to the Cac2 subunit of histone chaperone CAF-1 and the conformational changes allow the delivery of H3-H4 dimer from Asf1 to CAF-1, thus providing direct evidence for coordination between histone chaperones (Tyler et al., 2001; Mello et al., 2002). In addition to direct interaction between Asf1 and CAF-1, previous studies suggest that ubiquitination of H3K122 will destabilize the interaction between Asf1 and H3-H4 complex, which in turn facilitates the transfer of H3-H4 from Asf1 to CAF-1 (Han et al., 2013).

In yeast, yeast cells lacking CAF-1 are viable (Kaufman et al., 1997), suggesting that other histone chaperones likely promote deposition of new H3-H4 onto replicating DNA. Indeed, it has been shown that Rtt106 (Regulator of Ty1 transposon 106) functions in parallel with CAF-1 in deposition of new H3-H4 (Huang et al., 2005; Huang et al., 2007). In addition to CAF-1 and Rtt106, using a separation of functional mutant alleles, FACT has also been shown to function in the deposition of newly synthesized H3-H4 during replication (Yang et al., 2016). FACT contains multiple PH (pleckstrin homology) domains and can bind to H3-H4 with newly synthesized histone marks. Thus, multiple chaperones function in the deposition of new H3-H4 onto replicating DNA. Furthermore, in cells, these chaperones co-purify with each other. For instance, FACT can co-purify with CAF-1 and Rtt106, and the interaction between them is bridged by H3K56Ac and peaks during S phase (Yang et al., 2016). In addition, CAF-1 also co-purifies with Rtt106 (Huang et al., 2005). These physical interactions indicate that these chaperones form a coordination network for *de novo* histone deposition during S phase.

Histone modifications and variant amino acids on histone proteins regulate the interaction between newly synthesized histones and histone chaperones

Newly synthesized histones are also modified post-translationally and most of these modifications are distinct from modifications on parental histones. For instance, acetylation of histone H4 lysine 5 and 12 (H4K5,12) by HAT1-RbAp46 acetyltransferase and acetylation at some lysine residues on H3 tails (H3K4,9,14,23,27) are marks on newly synthesized histones across almost all species (Sobel et al., 1995; Verreault et al., 1996). In fungal species, H3K56ac is a mark on new H3 (Masumoto et al., 2005; Zhou et al., 2006). H3K56ac is catalyzed by the Rtt109-Vps75 complex and histone chaperone Asf1 is essential for H3K56 acetylation (Han et al., 2007a; Han et al., 2007b). The structure of Rtt109 in complex with Asf1-H3-H4 indicates that while Asf1 has little contact with Rtt109, it positions H3 lysine 56 for acetylation by Rtt109 (Zhang et al., 2018). In addition to histone acetylation, mono-methylation of histone H3K9 (H3K9me1) by SETDB1 is also found on H3.1 prior to deposition in mammalian cells (Loyola et al., 2006).

Several functions have been uncovered for the modifications on newly synthesized H3-H4. First, the acetylation of H4K5,12 occurs in cytoplasm and promotes the nuclear import of histone H3-H4 mediated by histone chaperone Asf1 and the Importin complex (Zhang et al., 2012; An et al., 2017). Importin Kap123 contains two lysine binding pockets, and acetylation at lysine residues on histone H3 and H4 weakens the interaction of H3-H4 with importin (An et al., 2017). Second, H3K56 acetylation regulates the interactions between H3-H4 and CAF-1 and Rtt106 (Chen et al., 2008; Li et al., 2008). Moreover, acetylation at both H3 and H4 tails also significantly increases the interaction of CAF-1 and Rtt106 with new H3-H4 and promotes replication-coupled nucleosome assembly (Burgess et al., 2010). Rtt106 contains two tandem PH domains that likely bind to H3K56 acetylated H3-H4 (Su et al., 2012). However, how CAF-1 recognizes H3K56ac and acetylates H3 and H4 tails remains to be determined. Furthermore, it remains unclear whether H3K56ac, which is present at low abundance in metazoans, also has a role in replication-coupled nucleosome assembly. Finally, it has been proposed that H3K9me1 helps the restoration of H3K9me2/me3 by serving as a substrate for H3K9 methyl-transferases that catalyze di- and tri-methylation (Loyola et al., 2006). For a detailed description of histone modifications' role in replication-coupled nucleosome assembly we refer readers to other reviews like "All roads lead to chromatin"(Li et al., 2013).

In addition to histone modifications, variant amino acids found on histone H3.1/H3.2 and H3.3 play a key role in regulating the interaction between H3-H4 and the corresponding histone chaperones. Histone H3.1/H3.2 differ from H3 variant H3.3 by four or five amino acids, with the three variant amino acids located at residues 87 to 90 (SAVM in H3.1/H3.2 vs. AAIG in H3.3). H3.1/H3.2 bind to histone chaperone CAF-1 and is deposited during S phase of cell cycle in the replication-coupled nucleosome assembly pathway (Ahmad and Henikoff, 2002a, 2022b). In contrast, H3.3 associates with histone chaperones HIRA and DAXX, and it can be deposited both during and outside of S phase (Tagami et al., 2004; Drané et al., 2010; Goldberg et al., 2010). Mutating the three variant amino acids between H3.1/H3.2 and H3.3 can alter their interactions with CAF-1 and/or HIRA/DAXX and subsequent deposition onto DNA (Lewis et al., 2010; Elsässer et al., 2012; Liu et al., 2012a). Finally, it has been shown that phosphorylation of H4 serine 47 inhibits the interaction between CAF-1 and H3-H4 and promotes the interaction between HIRA and H3-H4 (Kang et al., 2011). Together, these studies indicate that modifications on newly synthesized H3-H4 and variant amino acids on histone proteins regulate the dynamic interactions between histone and histone chaperones, thereby providing the supply of other half of histones for the assembly of newly replicated DNA into nucleosomes.

Histone chaperones connect to replication forks via interactions with replisome components

How do histone chaperones deposit newly synthesized H3-H4 specifically at replicated DNA? The answer to this question lies at least partially in the physical interactions between histone chaperones and replisome components. Early studies showed that CAF-1 interacts with PCNA (proliferating cell nuclear antigen) (Shibahara and Stillman, 1999). PCNA forms a homotrimer (Pol30 subunits in budding yeast) and functions as a sliding clamp for both Polδ and Polε involved in lagging and leading strand DNA synthesis, respectively (Choe and Moldovan, 2017). Depletion of PCNA inhibits CAF-1 mediated chromatin assembly *in vitro* (Shibahara and Stillman, 1999). Furthermore, site-specific PCNA mutations that disrupt the CAF-1-PCNA interaction in budding yeast, while showing minor effects on cell growth, result in defects in transcriptional silencing, in the same pathway as cells lacking CAF-1 (Zhang et al., 2000). A recent discovery found that introduction of the same PCNA mutations in mouse ES cells led to defects in differentiation *in vitro*, and embryonic lethality during mouse early development (Cheng et al., 2019). Together, these studies suggest that the PCNA-CAF-1 interaction is important for the deposition of new H3-H4 and embryonic development.

In addition to PCNA, RPA, the single-stranded DNA binding protein at the replication forks, can also interact with multiple histone chaperones. RPA contains three subunits named as Rfa1, Rfa2 and Rfa3 in budding yeast or RPA70, RPA32 and RPA14 in humans, respectively. RPA interacts with histone chaperones FACT, CAF-1 and Rtt106, but not Asf1 (Liu et al., 2017). Genetic analysis suggests the potential coordination between FACT and RPA during nucleosome assembly (VanDemark et al., 2006). Besides histone chaperones, RPA also binds to free histone H3-H4 directly but not intact nucleosomes or H2A-H2B (Liu et al., 2017). Furthermore, histone H3-H4 promotes the interaction of RPA with those histone chaperones. Moreover, RPA can also deposit H3-H4 onto adjacent double strand DNA when bound to ssDNA, indicating a role of RPA in histone deposition mediated by multiple histone chaperones (Liu et al., 2017). Finally, it has been shown that FACT co-purifies with MCM helicases in both yeast and mammalian cells (Gambus et al., 2006; Tan et al., 2006). Together, these studies indicate that histone chaperones involved in *de novo* deposition of new H3-H4 interact with multiple components of replisomes, which likely mediate the ability of these histone chaperones to deposit H3-H4 in the DNA replication-coupled process. However, the functional significance of several aforementioned interactions between histone chaperones and replisome components in replication-coupled nucleosome assembly remains to be determined.

General principles for the restoration of histone modifications following DNA replication

Early studies on X-chromosome inactivation, position effect variegation in *Drosophila*, genome imprinting, silent chromatin at mating type locus in both budding and fission yeast strongly support the idea that heterochromatin domains can be inherited through mitotic cell divisions. These studies were performed before the discoveries that distinct histone modifications mark active and repressive chromatin domains (Grewal and Jia, 2007).

It is well accepted that DNA methylation is heritable, however, it is clear that not all histone modifications are heritable for various reasons (Zhu and Reinberg, 2011; Ptashne, 2013; Reinberg and Vales, 2018). Currently, it is estimated that over 80–100 posttranslational modifications on four histone proteins can be identified (Zhao and Garcia, 2015). Some of these histone modifications such as acetylation are quite labile with a half-life less than one cell cycle (Zee et al., 2010). Therefore, it is unlikely that those labile histone modifications can be used as templates for the restoration of the modification following DNA replication without the aid of other factors. In addition, it is known that most nucleosomal H2A-H2B proteins exchange relatively freely with newly synthesized H2A-H2B within one cell cycle (Xu et al., 2010). Therefore, it is likely that most modifications on H2A-H2B might not be heritable. Of note, it has been recently shown that H2AK119 ubiquitination located at repressive heterochromatin can be inherited (Zhao et al., 2020a), suggesting that some H2A-H2B modifications are heritable. Compared with H2A-H2B, H3-H4 tetramers, once assembled into nucleosomes, are relatively stable and do not exchange freely with newly synthesized H3-H4. Indeed, methylation of H3 and H4, including H3K27me3 and H3K9me2/m3, are widely accepted as inheritable epigenetic marks (Margueron et al., 2009; Liu et al., 2015; Coleman and Struhl, 2017; Laprell et al., 2017) and have a half-life over one cell cycle. These findings suggest that histone modifications with longer half-life are more likely to be transmitted following DNA replication. Moreover, it is known that histone H3.1 at active or repressive chromatin regions shows distinct patterns following DNA replication (Escobar et al., 2019), suggesting that the heritability of histone modifications likely also depends on local chromatin environment. Therefore, future studies are warranted to explore the regulatory network that governs the inheritance of different epigenetic modifications.

An early insight into the inheritance of histone modifications came from studies on H3K27me3, which reported that EED, a subunit of the PRC2 complex catalyzing H3K27me3 (Margueron and Reinberg, 2011; Holoch and Margueron, 2017), has a chromodomain that recognizes H3K27me3. *In vitro* studies indicate that binding of H3K27me3 by EED

stimulates the enzymatic activity of PRC2 to methylate neighboring nucleosomes without this modification (Margueron et al., 2009). In mouse ES cells, mutations at EED chromodomain impairing its binding to H3K27me3 result in defects in the spreading of H3K27me3 (Oksuz et al., 2018). Similarly, G9a/GLP, the methyltransferases for H3K9me2, harbor ankyrin repeat domains, and the association of G9a/GLP with H3K9me2 also stimulates their enzymatic activities. Mice with mutations at GLP ankyrin repeat show defects in growth ossification and postnatal lethality (Liu et al., 2015). Moreover, Suv39h1/h2, the enzymes catalyzing H3K9me3 in mammalian cells, contain a chromodomain that recognizes H3K9me3, although the functional significance of this domain is not well explored. In fission yeast, the recognition of H3K9me2/me3 by the chromodomain of Clr4, the sole H3K9me3 writer, is important for inheritance of this mark (Ragunathan et al., 2015; Wang and Moazed, 2017). Together, these studies support a positive feedback model whereby H3K9 or H3K27 enzymes first recognize (read) their cognate modifications on nucleosomes from parental histones and then modify (write) nucleosomes containing newly synthesized histones without this mark following DNA replication (Figure 3).

It was proposed that repressive marks including H3K9me3 and H3K27me3 are inheritable (see discussion below), whereas active marks such as H3K4me3 are not (Reinberg and Vales, 2018). However, in the literature, there are examples that active chromatin domains are also heritable. For instance, it has been shown that the active gene state can persist through 24 cell divisions in the absence of gene transcription in nuclear transfer experiments and this epigenetic memory depends on the incorporation of H3.3, a histone H3 variant marking actively transcribed genes, as well as on H3.3 lysine 4 (Ng and Gurdon, 2008; Hörmanseder et al., 2017). In *C. elegans*, mutations at H3K4me3 methyltransferases result in increased life span, and this increase can be transmitted into descendants up to three generations, suggesting that certain chromatin loci marked by H3K4me3 can be maintained trans-generationally (Greer et al., 2011). In mouse mature oocytes, a non-canonical form of H3K4me3 that contains broad H3K4me3 peaks at the promoters and distal loci was discovered. These broad H3K4me3 domains can be inherited in post-fertilization embryos, before being erased at two cell embryo stages (Dahl et al., 2016; Zhang et al., 2016). These studies strongly suggest that active marks such as H3K4me3 may also be inherited under certain conditions. Supporting this idea, the Spp1 (CFP1 in humans), a subunit of the COMPASS complex that catalyzes H3K4me3, also contains a PHD domain that binds to H3K4me3 (He et al., 2019). Indeed, it has been recently shown that both gene transcription machinery and the read of H3K4me3 by Spp1 help recruit the COMPASS complex for the restoration of H3K4me3 following DNA replication (Serra-Cardona et al., 2022).

The read-write mechanism is just one part of the puzzles for the restoration of histone modifications following DNA replication. In fact, the inheritance of histone modifications is much more complicated. For instance, it has been shown that different histone modifications are restored on newly synthesized histones at different rates following DNA replication. Moreover, while restoration of histone modifications may start at S phase of the cell cycle, it takes until next G1 for cells to fully restore most histone modifications (Xu et al., 2011; Alabert et al., 2015). Furthermore, the cis-regulatory element called PRE involved in the establishment of H3K27 methylation in early embryo is needed for the stable maintenance of this mark, most likely through recruiting PRC2 along with the read-write mechanism, to methylate H3K27 in nucleosomes formed with newly synthesized H3-H4 following DNA replication (Coleman and Struhl, 2017; Laprell et al., 2017). Moreover, when the PRE is removed, there is still considerable, residual capacity for copying the mark, likely due to the function of the read-write mechanism (Coleman and Struhl, 2017). In *S. pombe* and as described in detail in the next section, both cis-regulatory elements and RNAi machinery play important roles in the inheritance of H3K9 methylation.

Several factors likely contribute to the complex nature for the stable inheritance of histone modifications. First, compared to DNA sequences, histone modifications are reversible due to the presence of eraser proteins, providing a balance and competition between writers and erasers for a particular histone modification. Therefore, in principle, cells need to increase the local concentration of writers and/or reduce the concentration of the erasers for the histone modifications in order to faithfully maintain them during cell division. Second, there are cross-talks among histone modifications at different chromatin regions. For instance, H3K36 methylation, an active mark, can counterbalance H3K27 methylation, a silent chromatin mark (Yuan et al., 2011). Therefore, an increase in the concentration of writers/erasers for H3K36 methylation can in principle influence the dynamics of H3K27 methylation, or *vice versa*. Third, some histone modifications such as H3K4me3 are deposited co-transcriptionally (Soares et al., 2017; Bae et al., 2020). Moreover, ongoing transcription can promote active histone turnovers, i.e., exchange between parental histones and newly synthesized histones. Therefore, it is proposed that factors inhibiting histone turnover/exchange likely play an important role in epigenetic inheritance (Aygün et al., 2013). Finally, there are cross-talks between histone modifications and DNA methylation (see detailed discussion below). Because of these complications, we propose that the restoration of histone modifications following DNA replication requires the interplay of histone modifications, cis-regulatory DNA elements, non-coding RNA and DNA methylation.

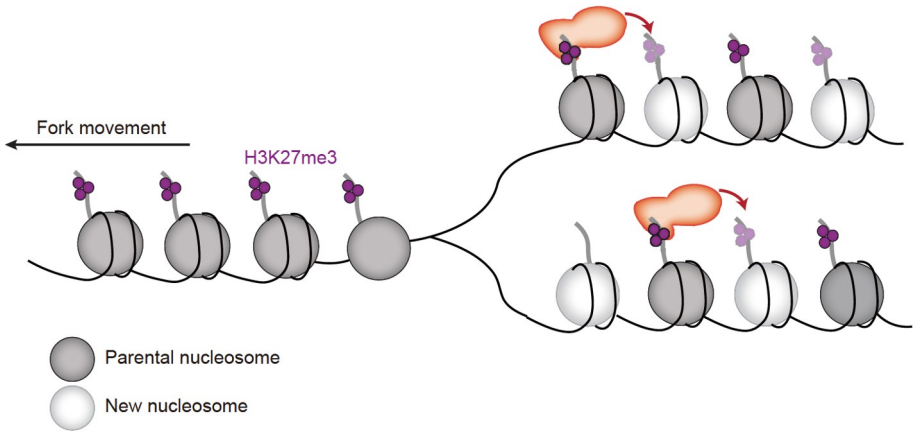

Figure 3 The read and write mechanism contributes to the restoration of key histone modifications following DNA replication. Please note that the restoration of histone modifications starts during S phase and may last till G1 phase of the cell cycle.

Below, we use the inheritance of H3K9 methylation in *S. pome* as the model to discuss these ideas for the following reasons. First, key factors involved in H3K9 methylation and heterochromatin assembly are highly conserved in higher organisms. Second, the genetic power of yeast system allows precise genetic manipulations. Third, heterochromatin proteins are not essential for cell viability, allowing greater flexibility for genetic analyses. Fourth, there is usually a single gene encoding H3K9 heterochromatin regulators, avoiding complications from multiple proteins with partially overlapping functions. Finally, fission yeast does not have DNA methylation. Together, this system makes it possible to dissect the molecular mechanisms underlying the inheritance of heterochromatin marked by H3K9 methylation.

Inheritance of H3K9 methylation, a lesson learned from *S. pombe*

In fission yeast, large heterochromatin domains are present at the pericentric region, silent mating-type region, and subtelomeres (Grewal and Jia, 2007). These regions all contain repetitive DNA sequences, and the formation of heterochromatin is critical for suppressing recombination between repeats to maintain genome stability. Heterochromatin also silences the transcription of genes within and near it in a sequence-independent manner to regulate gene expression programs.

Nucleosomes within these heterochromatic regions are methylated at histone H3 lysine 9 (H3K9me). H3K9me recruits heterochromatin protein 1 (HP1) family proteins Swi6 and Chp2, which in turn recruit diverse proteins to regulate different biological processes (Grewal and Jia, 2007). Clr4 is the sole histone H3K9 methyltransferase critical for heterochromatin formation (Rea et al., 2000; Nakayama et al., 2001), which contains a SET domain that catalyzes H3K9me, and a chromodomain that recognizes H3K9me3 (Zhang et al., 2008). Mutations of the chromodomain that affect Clr4 interaction with H3K9me3 reduced binding of Clr4 to its target sites, and H3K9me3 domains are no longer properly inherited. These results support the idea that Clr4 not only "writes" H3K9me3 but also "reads" it, forming a positive feedback loop. The coupling of "read" and "write" activities is also critical for restoring H3K9me3 domain after DNA replication, where parental histones containing H3K9me3 serve as seeds for the recruitment of Clr4 to modify newly synthesized histones.

Early studies of heterochromatin at the silent mating-type locus established that heterochromatin can be epigenetically inherited, even before the role of histone H3K9 methylation in heterochromatin assembly has been discovered. Fission yeast has two different mating types: P (plus) and M (minus). The mating type of a cell is determined by the gene content within the *mat1* locus, which is actively transcribed (Figure 4). Cells can also switch their mating types using one of the two donor sequences, *mat2P* or *mat3M*, located more than 10 kilobases away from *mat1*. The donors, as well as the sequences between them, are silenced by heterochromatin. Among the sequences between donors is *cenH* (centromere homology), which is homologous to pericentric repeats. Replacing *cenH* with a *ura4*$^+$ reporter gene leads to cells with one of two stably maintained states: "*ura4-on*" (the reporter is expressed) and "*ura4-off*" (the reporter is repressed) (Grewal and Klar, 1996) (Figure 4A). Due to the low switching rate from *ura4-on* to *ura4-off*, heterochromatin of *ura4-off* cells is presumed to be maintained in the absence of *de novo* establishment. Genetic analyses demonstrate that these epigenetic states are inherited through both mitosis and meiosis, behaving similarly to gene alleles (Grewal and Klar, 1996). Later it was demonstrated that the two epigenetic alleles are different in their chromatin environments, such as H3K9 methylation and Swi6 protein levels (Nakayama et al., 2000; Hall et al., 2002).

The *cenH* sequence as well as pericentric repeats are later

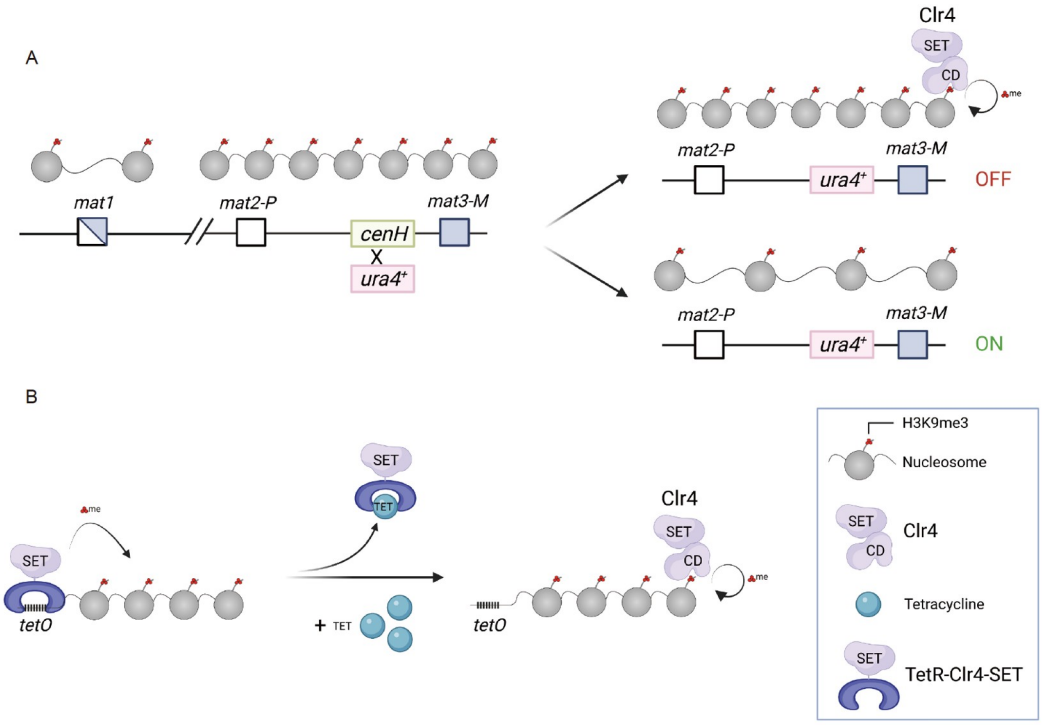

Figure 4 Epigenetic inheritance of H3K9me3 in *S. Pombe*. A, At the silent mating-type region, the replacement of *cenH* with a *ura4*$^+$ reporter results in two metastable epigenetic states: *ura4-on* and *ura4-off*. The *ura4-off* state can be maintained during mitosis and meiosis through the coupling of "read-write" activities of Clr4. B, The *tetO* sites recruit TetR-Clr4-SET to establish ectopic heterochromatin. The addition of tetracycline release TetR-Clr4-SET and heterochromatin is maintained by endogenous Clr4.

found to initiate heterochromatin formation through the RNA interference (RNAi) pathway (Hall et al., 2002; Volpe et al., 2002). The DNA repeats are transcribed, generating double-stranded RNAs (dsRNAs) (Volpe et al., 2002), which are processed by the ribonuclease Dicer (Dcr1) into small interfering RNAs (siRNAs). The Argonaute protein (Ago1) within the RNA-induced transcriptional silencing complex (RITS) binds to siRNAs and directs RITS to nascent RNA transcripts originated from repeat regions (Motamedi et al., 2004; Verdel et al., 2004). RITS then recruits the CLRC complex, which contains the H3K9 methyltransferase Clr4, to initiate H3K9me3 (Zhang et al., 2008; Bayne et al., 2010; Gerace et al., 2010). Therefore, *cenH* is critical for the initial RNAi-mediated targeting of Clr4 to the mating-type region to establish heterochromatin. But once formed, this heterochromatin is efficiently inherited by subsequent generations even in the absence of *cenH* and RNAi.

However, such a simplified explanation is complicated by later findings that transcription factors Atf1/Pcr1 recognize target sequences within the silent mating-type region and cooperate with RNAi to recruit Clr4 to establish heterochromatin (Jia et al., 2004; Kim et al., 2004; Wang and Moazed, 2017; Wang et al., 2021). Although Atf1/Pcr1 binding sites cannot independently initiate heterochromatin formation, it still raises concern that removal of *cenH* does not completely abolish heterochromatin establishment. To precisely measure heterochromatin inheritance in the absence of *de novo* establishment, ectopic heterochromatin is established by recruiting a TetR and Clr4-SET domain (TetR-Clr4-SET) fusion protein to *tetO* binding sites, leading to the silencing of adjacent report genes (Audergon et al., 2015; Ragunathan et al., 2015) (Figure 4B). Releasing TetR-Clr4-SET from *tetO* binding sites by the addition of tetracycline allows the examination of heterochromatin maintenance through the self-templated restoration of H3K9me3 by endogenous Clr4. This artificial heterochromatin can persist after TetR-Clr4-SET release, although only after removing an anti-silencing protein Epe1. Moreover, the inheritance of such chromatin structure is dependent on the ability of the Clr4 chromodomain to recognize H3K9me3 (Audergon et al., 2015; Ragunathan et al., 2015). These results clearly demonstrate that cells can indeed mediate epigenetic inheritance of H3K9me3 marked chromatin by coupling the "reading" and "writing" of H3K9me3. However, they also indicate that this mechanism alone is not sufficient to maintain heterochromatin states because of other mechanisms that counter the inheritance of H3K9 methylation, such as Epe1.

Epe1 contains a JmjC domain, which typically catalyzes histone demethylation (Tsukada et al., 2006). However, no demethylase activity of Epe1 has been demonstrated *in vitro*, and the commonly used mutations expected to abolish Epe1

demethylase activity actually influence protein-protein interactions (Raiymbek et al., 2020). Moreover, Epe1 is known to exert its function on heterochromatin independent of its JmjC domain (Wang et al., 2013; Bao et al., 2019; Sorida et al., 2019). Therefore, the mechanisms whereby Epe1 counteracts histone-based heterochromatin maintenance remain unclear.

In addition to Epe1, other mechanisms that counteract heterochromatin inheritance have also been uncovered. At pericentric repeats, RNAi is the major pathway to establish heterochromatin. However, heterochromatin is not properly maintained in RNAi mutants, consistent with the existence of mechanisms that counteract heterochromatin inheritance. Interestingly, mutations of the Mst2 histone acetyltransferase complex, INO80 chromatin remodeling complex, the Paf1C complex associated with transcription, or Epe1 bypass RNAi for heterochromatin inheritance (Trewick et al., 2007; Reddy et al., 2011; Ragunathan et al., 2015; Sadeghi et al., 2015; Shan et al., 2020). A common theme is that all of them promote histone turnover at heterochromatin (Aygün et al., 2013; Sadeghi et al., 2015; Wang et al., 2015; Shan et al., 2020). A higher histone turnover rate leads to the loss of the parental histones containing H3K9me3 at the original location after DNA replication, therefore breaking the read-write cycle for chromatin-based epigenetic inheritance (Shan et al., 2021). As a result, RNAi is constantly needed to maintain a high concentration of Clr4 to counteract the loss of parental histones by histone turnover. Supporting this idea, the coupling of siRNA production and H3K9me positive feedback loops also promotes the inheritance of ectopic heterochromatin induced by siRNAs (Yu et al., 2018b). Therefore, faithful inheritance of H3K9me3 marked chromatin in fission yeast adopts multiple approaches including the read-write mechanism (Wang et al., 2018a), inhibition of histone turnover, and an increase in the local concentration of H3K9 methyltransferase via the RNAi machinery and DNA sequence-specific binding proteins.

DNA methylation inheritance including *de novo* deposition and maintenance of DNA methyltransferases

In mammals, DNA methylation primarily occurs on the fifth position of cytosine (5-methylcytosine) in the palindromic CpG context, and DNA methylation is one of the well-studied epigenetic modifications. DNA methylation plays important roles in stably silencing the inactivated X chromosome, repetitive elements, imprinting genes and developmental genes. Long-term transcription repression effect of DNA methylation is mediated by recruiting methyl-CpG-binding protein 2 (MECP2) in complex with histone deacetylases (HDACs), which reduce chromatin accessibility and cause local condensation (Jones et al., 1998; Nan et al., 1998; Muotri et al., 2010). Alternative silencing strategy of DNA methylation is to prevent methylation-sensitive transcription factors (TFs) from binding to their cognate sequences (Tate and Bird, 1993). Besides, DNA methylation could stably repress gene expression during mitosis and confer plasticity upon stimulation, suggesting that DNA methylation can also serve as an epigenetic marker for regulation of epigenetic transcriptional memory described below.

DNA methylation is catalyzed by DNA methyltransferases (DNMTs) in mammalian cells, and cytosines in CpG palindrome can be unmethylated, hemi-methylated or fully-methylated at various genomic regions. Based on the preference of the methylated state of cytosine substrates, DNMTs are classified into two groups: maintenance DNA methyltransferase (DNMT1) that shows selective activity toward hemi-methylated CpG substrates, and *de novo* DNA methyltransferases (DNMT3A, DNMT3B and rodent specific DNMT3C) that exhibit comparable activity on both unmethylated and hemi-methylated substrates (Figure 5).

In the early studies, DNMT1 was defined as maintenance DNA methyltransferase based on its preferential activity on hemi-methylated CpGs (Bestor et al., 1988; Pradhan et al., 1999). However, recent studies challenged this simple classification model of DNMTs. Firstly, biochemical results identified considerable *de novo* methyl-transfer activity of DNMT1 on unmethylated substrates (Bestor and Ingram, 1983; Jeltsch and Jurkowska, 2014). Further *in vivo* studies confirmed the notable *de novo* activity of DNMT1 enzyme. In oocytes depleted of *Stella*, which is a maternal factor essential for early development, DNMT1 was aberrantly accumulated at vast chromatin regions, with significant *de novo* methyl-transfer activities (Li et al., 2018b). This activity was also observed in *"Dnmt1"* only oocytes (i.e., oocytes with naturally silenced *Dnmt3b* and genetically depleted *Dnmt3a*) (Li et al., 2018b), further confirming the *de novo* activity of DNMT1. Furthermore, a well-designed hairpin-bisulfite sequencing study identified about 0–5% *de novo* activity of DNMT1 during replication-coupled phase (Ming et al., 2021a). Moreover, although DNMT3s mainly work as *de novo* methyltransferase, they lack selectivity toward unmethylated and hemi-methylated CpG dinucleotide substrates. Hairpin-bisulfite sequencing found significant fully-methylated CpG sites in *Dnmt1* depleted ESCs (Arand et al., 2012), indicating DNMT3s also contribute to DNA methylation maintenance *in vivo*. Finally, DNMT3 enzymes could fill gaps caused by inefficiency of DNMT1 and counteract demethylation mediated by ten-eleven translocation (TET) enzymes (Ramsahoye et al., 2000; Liang et al., 2002; Jackson et al., 2004). Thus, DNMT1 and DNMT3 enzymes are both responsible for considerable *de novo* deposition and maintenance of DNA methylation, at least in some cellular contexts (Ming et al., 2021b). Consistent with

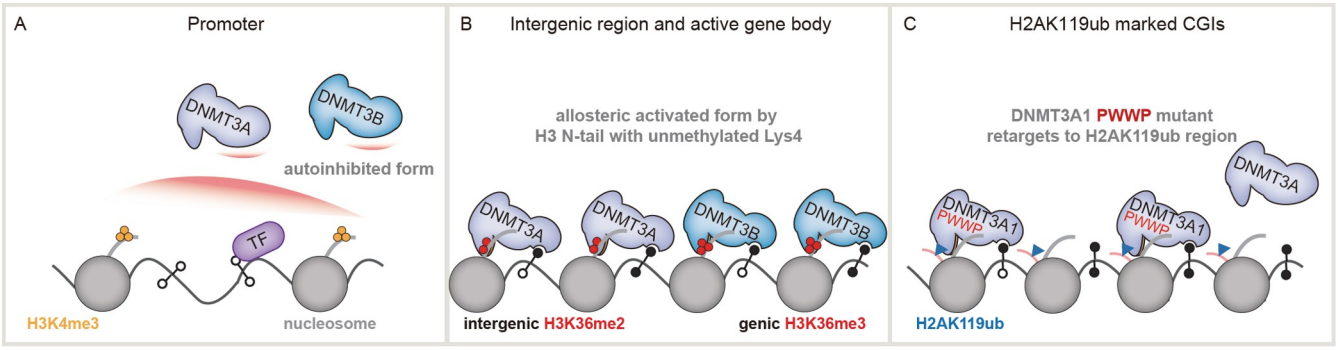

Figure 5 Dynamic interplays between histone modifications and DNA methylation.

this idea, these enzymes show context dependent functions in mammalian development. It would be interesting for future studies to dissect the contribution of *de novo* deposition and maintenance activity of different DNMTs at different developmental stages or pathological contexts. We will focus on discussing latest findings on mechanisms of DNA methylation inheritance, the crosstalk between DNA methylation and histone modifications, and the role of DNA methylation in epigenetic transcriptional memory.

Dynamics of DNA methylation inheritance

Globally, genomic DNA methylation exhibits a bimodal distribution pattern in mammalian cells. Most genomic CpG sites are hypermethylated, however, a fraction of CpG sites residing in CG-dense DNA sequences named CpG islands (CGIs) are generally hypomethylated (Cooper et al., 1983; Bird et al., 1985). CGIs predominantly localize at regions nearby the transcription start sites (TSSs) or promoters of house-keeping genes and developmental genes. In addition, many regulatory elements used to control gene expression are largely resistant to CpG methylation (Hon et al., 2013; Ziller et al., 2013; Rasmussen and Helin, 2016). The bimodal landscape of mammalian methylome is a result of the dynamic balance between DNA methylation and demethylation activities. During development, bulk genomic DNA methylation pattern is static upon differentiation, and demethylation only occurs at specific sites in response to certain cellular signals. In contrast, global DNA demethylation happens in primordial germ cell (PGC) specification stage and pre-implantation embryos to reset the methylome pattern. In general, DNA methylation inheritance during mitotic cell division is sophisticatedly regulated by multiple mechanisms: chromatin targeting and activity control of DNMTs to counterbalance the effects of imperfect maintenance efficiency of DNMT1 and demethylation mediated by TET family enzymes. Moreover, DNA methylation maintenance is mainly a regional regulatory event (Wang et al., 2020; Ming et al., 2021a) as local chromatin environment including histone modifications and neighboring CpG state (CpG densities and methylation levels) are important for the dynamic turnover and inheritance of mammalian DNA methylome.

Maintenance of DNA methylation during mitotic cell division

Recent studies indicated that maintenance methylation occurred quickly in a replication-coupled manner, with approximately 50% of the CpG sites methylated within minutes and 80% of the sites within 30 min after DNA replication. However, restoration of DNA methylation following DNA replication also occured outside the S phase (replication-uncoupled phase) (Figure 6) (Charlton et al., 2018; Xu and Corces, 2018; Ming et al., 2021a). To achieve these, mammals have evolved multiple mechanisms to ensure the fidelity and robustness of DNA methylation maintenance. For instance, during mitotic cell division, the chromatin targeting activity and protein stability of DNMT1 are regulated to safeguard DNA methylation maintenance. Several key cofactors, such as PCNA, LIG1 (DNA ligase 1), UHRF1 (ubiquitin-like with PHD and RING finger domains 1), PAF15 (PCNA associated factor 15) and LSH (lymphoid-specific helicase), are required for the maintenance role of DNMT1. During replication-coupled phase, the highly efficient maintenance activity of DNMT1 relies on its connection with DNA replication forks mediated by multiple protein-protein interactions including PCNA-DNMT1, UHRF1-LIG1 and ubiquitinated H3-DNMT1 interactions. DNMT1 interacts with PCNA, a DNA clamp tethering DNA polymerases to DNA replication forks, through PBD domain (PCNA binding domain) (Chuang et al., 1997; Egger et al., 2006). PAF15 contains a N-terminal H3-like sequence that could be ubiquitinated at Lys 15 and Lys 24 by UHRF1 (Karg et al., 2017), and ubiquitinated PAF15 binds to the replication focus targeting sequence (RFTS) of DNMT1, which facilitates the association of DNMT1 with replisomes (González-Magaña et al., 2019; Nishiyama et al., 2020). LIG1 is a component of the replication machinery and is responsible for ligating Okazaki fragments, of which the Lys 126 (K126)

and surrounding residues mimicked histone H3K9 site (Ferry et al., 2017) that can be methylated by G9a/GLP. UHRF1 could bind to methylated LIG1 K126 to contact with replication fork and promote maintenance of the lagging strand (Ferry et al., 2017). These interactions together facilitate the efficient methylation maintenance function of DNMT1 in the replication-coupled phase (Figure 6A).

UHRF1 participates in DNA methylation maintenance through both replication-coupled phase and replication-uncoupled maintenance phase (Figure 6B) (Ming et al., 2021a). Early studies found that UHRF1 was essential for genomic DNA methylation inheritance by recruiting DNMT1 to methylated sites (Bostick et al., 2007; Sharif et al., 2007). UHRF1 contains several chromatin targeting domains, which function cooperatively to promote proper chromatin targeting of UHRF1 (Arita et al., 2012; Cheng et al., 2013; Rothbart et al., 2013; Vaughan et al., 2018). The SET and RING-associated (SRA) domain shows higher binding selectivity towards hemi-methylated CpG sites (hemi-mCG), which are established after DNA replication (Avvakumov et al., 2008; Hashimoto et al., 2008; Qian et al., 2008; Fang et al., 2016). The tandem tudor (TTD) domain of UHRF1 shows high affinity to H3K9me2/3 modification, and the plant homeodomain (PHD) domain prefers the H3 N-tail with unmethylated H3R2 (Rajakumara et al., 2011; Arita et al., 2012; Cheng et al., 2013). Recognition of H3K9me2/3 modified nucleosome is mediated by cooperative binding of TTD and PHD (Cheng et al., 2013; Rothbart et al., 2013). Thus, UHRF1 could be recruited to DNA replication foci at heterochromatin through the UHRF1-LIG1 interaction, recognition of hemi-mCG by SRA domain and the interaction between TTD-PHD domain of UHFR1 and H3K9me2/3. Moreover, the TTD domain of UHRF1 and its recognition of H3K9me2/3 modification are critical also for replication-uncoupled DNA maintenance (Ming et al., 2021a). UHRF1 contains a RING-finger E3 ligase domain, which is responsible for histone H3 ubiquitination (Nishiyama et al., 2013; Qin et al., 2015), and the hydrophobic patch of the ubiquitin-like (UBL) domain of UHRF1 is required for efficient H3 ubiquitination, mainly through stabilizing the E2/E3/chromatin complex (Foster et al., 2018). Early studies proposed that UHRF1 facilitates methylation maintenance activity of DNMT1 through recruiting of DNMT1 to replication forks (Bostick et al., 2007; Sharif et al., 2007). However, recent works indicated that ubiquitinated histone by UHRF1 could also promote DNMT1 recruitment and activate its methyltransferase activity (Nishiyama et al., 2013; Qin et al., 2015; Ishiyama et al., 2017; Foster et al., 2018; Li et al., 2018a). After DNA replication, many hemi-CG sites were hindered by histones and other chromatin proteins. Research found that chromatin remodeler LSH might function in remodeling nucleosomal CpG sites to expose them to DNMT1 (Dennis et al., 2001). LSH could promote nucleosomal CpG methylation maintenance in replication-uncoupled phase, especially in heterochromatin regions. Besides, LSH also associates with UHRF1, which could assist the UHRF1-DNMT1 DNA methylation maintenance pathway(Han et al., 2020). Among all co-factors of DNMT1, UHRF1 appears to be the most important co-factor for the maintenance of DNA methylation, as *Uhrf1* depletion dramatically damages the pattern and kinetics of the maintenance of DNA methylation, comparable to *Dnmt1* knockout.

Mechanisms for restricting excessive activity of DNMT1

Multiple mechanisms are evolved to restrict the activity of DNMT1 to avoid accumulation of aberrant DNA methylation at unmethylated sites through its *de novo* methylation activity. First, the protein levels of both DNMT1 and its key

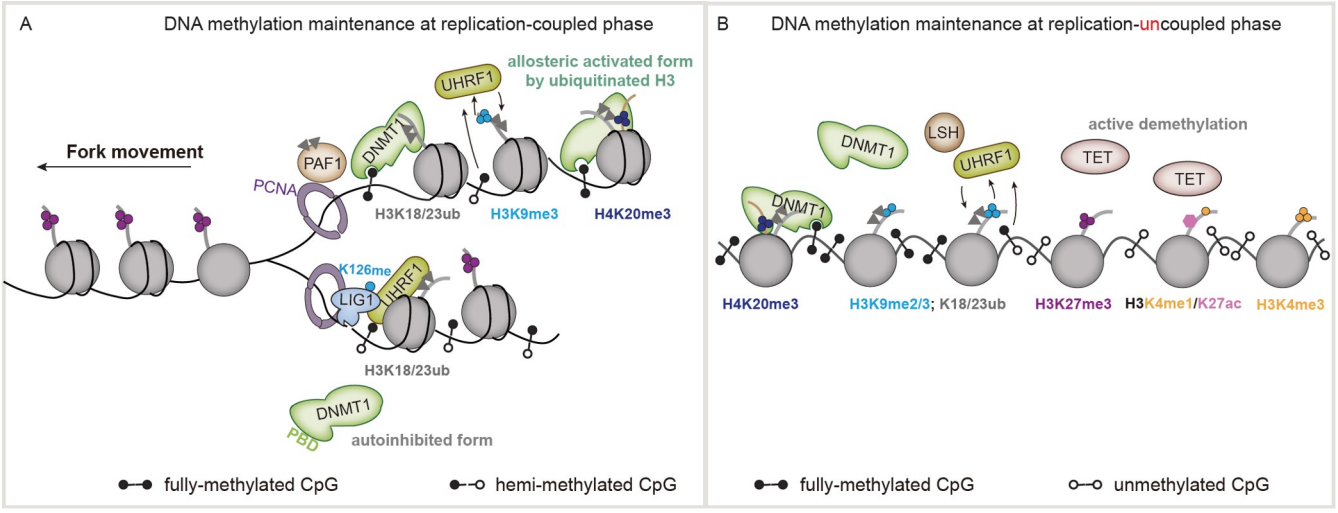

Figure 6 Epigenetic inheritance of DNA methylation.

cofactor UHRF1 are cell-cycle regulated. It was reported that DNMT1 stability is regulated by a series of integrated post-translational modifications, including methylation (Estève et al., 2009; Estève et al., 2011), acetylation (Du et al., 2010), and phosphorylation (Estève et al., 2011), which co-ordinately determine DNMT1 ubiquitination levels and protein stability. Methyltransferase SET7/9 methylates DNMT1 and triggers poly-ubiquitination and degradation of DNMT1 (Estève et al., 2009; Estève et al., 2011), whereas lysine-specific demethylase 1 (LSD1) stabilizes DNMT1 proteins, likely through demethylation (Zhang et al., 2019). Previous studies reported that AKT1 kinase phosphorylates DNMT1 Ser143 and interferes with lysine 142 methylation by SET7/9 (Estève et al., 2011). Therefore, the interplay of these two modifications affects cellular DNMT1 stability. Another study identified that cell-cycle regulated methyltransferase SET8/PR-Set7 could control the stability of both DNMT1 and UHRF1 through its methylation activity, followed by subsequent poly-ubiquitination mediated protein degradation (Zhang et al., 2019). SET8/PR-Set7 could down-regulate UHRF1 in G2/M phase, causing repression of the activity of DNMT1 on post-replicated DNA (Zhang et al., 2019). Thus, SET8/PR-Set7 and LSD1 compete to regulate genomic DNA methylation, most likely through regulation of UHRF1 protein levels. DNMT1 could be acetylated by acetyltransferase TIP60 for subsequent ubiquitination and proteasomal degradation (Du et al., 2010). On the contrary, histone deacetylase 1 (HDAC1) and deubiquitinase could stabilize cellular DNMT1 levels (Du et al., 2010; Cheng et al., 2015). The acidic pocket in ubiquitin-specific protease 7 (USP7) interacts with lysine residues within KG linker of DNMT1, and this interaction is important for USP7 mediated DNMT1 stabilization (Cheng et al., 2015). Acetylation of lysine residues in DNMT1 KG linker interferes its binding to USP7, thus promoting ubiquitination and degradation of DNMT1 (Cheng et al., 2015). Besides, multiple-interaction networks among DNMT1, UHRF1, PCNA, LIG1, PAF15, LSH and histone H3 ubiquitination not only facilitate the sophisticated contact of DNMT1 with the replication fork in the replication-coupled phase, but also promote its targeting to sites for methylation in the replication-uncoupled phase. For instance, the specific binding between the SRA domain of UHRF1 and hemi-methylated CpG ensures DNMT1 to predominantly function as a maintenance methyltransferase. The interaction between the TTD-PHD module of UHRF1 and H3K9me2/3 helps to confer some degree of targeting specificity for DNMT1 (Cheng et al., 2013; Rothbart et al., 2013). Importantly, DNMT1 mediated methylation maintenance heavily relies on H3 ubiquitination, which has a fast turnover rate and is removed by USP7 after DNMT1 recruitment (Nishiyama et al., 2013; Yamaguchi et al., 2017). Interestingly, the *de novo* methylation activity of DNMT1 has to be tightly controlled. For example, during oocyte maturation, Stella is required to prevent aberrant accumulation of DNA methylation mediated by the *de novo* methylation activity of DNMT1, via disrupting the chromatin association of UHRF1 (Li et al., 2018b; Du et al., 2019). It is interesting to investigate whether the *de novo* methylation activity of DNMT1 is also under tight control in other post-mitotic cells that may allow aberrant methylation accumulation by the weak *de novo* methylation activity of DNMT1, especially during aging. Finally, DNA methylation maintenance efficiency is affected by the methylation levels of nearby CpG sites, which ensures the robustness in maintaining a bistable system that allows faithful maintenance of highly methylated regions and unmethylated regions, but not intermediately methylated regions (Ming et al., 2021a).

Crosstalk between DNA methylation and histone modifications

Somatic DNA methylation is set up *de novo* at early embryo development and maintained during subsequent mitotic cell cycles. Recent studies revealed complicated interplay between DNA methylation and histone modifications. As detailed below, some histone modifications help to recruit DNMTs to certain genomic regions and boost their methyltransfer activities, while others exclude them from chromatin with certain genomic features and suppress their catalytic abilities. Moreover, transitions from histone modification to DNA methylation were also observed in some processes including X-chromosome inactivation. For instance, during early stage of X-chromosome inactivation, H3K27 methylation by PRC2 complex silences one of the two X chromosome in female mammals, and this silencing mechanism is replaced by promoter DNA methylation during later stage of this process (Avner and Heard, 2001; Csankovszki et al., 2001; Sado et al., 2004; Disteche and Berletch, 2015; Pinter et al., 2012). Interestingly, inactivated X-chromosome was globally hypomethylated due to reduced H3K36 methylation caused by transcriptional silencing, except for promoter regions.

H3K4 methylation counters DNA methylation

DNA methylation is largely excluded from H3K4 methylation marked regions, such as active gene promoters and enhancers. In recent years, a series of studies revealed the underlying mechanism whereby H3K4 methylation repels the deposition of DNA methylation. DNMT3L is an enzymatically inactive homolog of DNMT3A and DNMT3B, and is required for establishing the DNA methylation landscape during gametogenesis (Bourc'his et al., 2001). Moreover, DNMT3L was reported to stimulate the activity of DNMT3A (Chedin et al., 2002). Structure analysis indicates that DNMT3L forms a functional heterotetramer with DNMT3A to promote *de novo* DNA methylation (Jia et al.,

2007), and this interaction also prevents the oligomerization of DNMT3A (Jurkowska et al., 2011). DNMT3L binds to the N-terminal H3 sequence, and this interaction was specifically suppressed by H3K4 methylation both *in vitro* and *in vivo* (Figure 5A) (Ooi et al., 2007). The DNMT3A-DNMT3L structural data indicates that DNMT3L binds to unmethylated H3 tail and promotes *de novo* DNA methylation through either enhancing the recruitment or activation of DNMT3A (Ooi et al., 2007). Another structural study found that the ATRX-DNMT3-DNMT3L (ADD) domain of DNMT3A also specifically binds to H3 N-tail without H3K4 methylation (Otani et al., 2009), suggesting ADD might recognize the unmethylated state of H3K4 and help DNMT3A to target chromatin properly. Methylation analysis using *in vitro* reconstituted chromatin showed that full-length DNMT3A and full-length DNMT3A/3L complexes methylate DNA, preferentially at linker DNA regions, of H3K4-unmethylated chromatin more efficiently than H3K4me3 marked chromatin (Zhang et al., 2010). The authors concluded that the improved activity of DNMT3A on H3K4-unmethylated chromatin was due to the selective binding property of ADD domain to H3K4-unmethylated region. Supporting this idea, the activity of catalytic domain of DNMT3A was not affected by H3K4me3 per se (Zhang et al., 2010). However, it is still unclear whether unmethylated H3 tail could induce allosteric activation of functional DNMT3A complex. Strikingly, an independent study showed that the activity of DNMT3A was stimulated by up to 8-fold by H3K4-unmethylated H3 tail (Li et al., 2011). However, the underlying molecular mechanism of allosteric regulation remains elusive. The autoinhibitory DNMT3A-DNMT3L complex and catalytically active DNMT3A-DNMT3L-H3 complex helped to clarify this issue. In the autoinhibitory structure, ADD domain of DNMT3A suppresses the methylation activity of DNMT3A by binding to catalytic domain (CD) of DNMT3A and thereby blocking DNA binding of CD (Guo et al., 2015). Histone H3 tail with unmethylated state of H3K4 specifically disrupts the ADD-CD interaction, and therefore release the autoinhibitory effects of DNMT3A (Guo et al., 2015). These studies provide a new insight in understanding the mutually exclusive genomic distribution of DNA methylation and H3K4 methylation. H3K4 methylation at promoters might be a potential mechanism for excluding DNA methylation at CGIs, however, mechanisms that maintain the hypomethylated state of CGIs are still elusive. It is proposed that transcription factors (Brandeis et al., 1994; Macleod et al., 1994), active demethylation by TET enzymes (Williams et al., 2012; Putiri et al., 2014; Verma et al., 2018) and skewed GC distribution nearby TSS (Ginno et al., 2012) all contribute to this process. In contrast to *Dnmt3a* or *Dnmt3b* deficient mice, *Dnmt3l* knockout mice are viable (Okano et al., 1999; Bourc'his et al., 2001). The functional requirement of DNMT3L for *de novo* methylation *in vivo* is still not fully answered.

Although DNMT3A is generally depleted at CGIs, it has been found that mutations at PWWP domain result in redistribution of DNMT3A to genomic regions including CGIs marked by ubiquitinated H2AK119 (Figure 5C) (Remacha et al., 2018; Heyn et al., 2019; Weinberg et al., 2021). The amino terminus of DNMT3A1 interacts with H2AK119ub-marked nucleosomes, serving as another chromatin targeting strategy for DNMT3A1 (Weinberg et al., 2021). This novel interaction explains the aberrant genomic distribution of DNMT3A and hypermethylation at Polycomb-regulated regions in paragangliomas and microcephalic dwarfism containing mutations at the PWWP domain of DNMT3A. In the future, it would be interesting to determine whether the N-terminus of DNMT3B and the tissue-specific or cancer-specific DNMT3A/3B isoforms (Chen et al., 2002; La Salle and Trasler, 2006; Gopalakrishnan et al., 2009; Duymich et al., 2016) also utilize similar strategies for chromatin targeting.

Different methylation state of H3K36 dictates chromatin targeting of DNMT3A and DNMT3B

For many years, the PWWP domain of DNMT3A/3B has been linked to chromatin targeting. PWWP domain, which contains a conserved aromatic cage for recognition of methylated lysine residue, is important for protein chromatin targeting through synergistic binding of histone and DNA (Wu et al., 2011; Qin and Min, 2014; Dukatz et al., 2019). Early study demonstrated PWWP domains are important for targeting DNMT3A/DNMT3B to major satellite regions (Chen et al., 2004; Ge et al., 2004). Loss of DNA methylation at satellite sequences was found in genetic diseases bearing PWWP mutations, such as ICF (immunodeficiency, centromere instability and facial anomalies) syndrome (Shirohzu et al., 2002). Together, these reports link the chromatin recruitment of DNMT3A/3B through the PWWP domain. Biochemical and structural studies indicate that PWWP domain of DNMT3A/3B interacts with H3K36me3 (Dhayalan et al., 2010; Qin and Min, 2014; Rondelet et al., 2016). Genomic binding profile studies found that DNMT3B is preferentially recruited to transcribed gene bodies, which are enriched with active H3K36me3 mark mediated by SET domain containing 2 (SETD2) (Figure 5B) (Sun et al., 2005; Edmunds et al., 2008; Baubec et al., 2015). SETD2 and PWWP domain are both required for proper targeting of DNMT3B to active gene bodies (Baubec et al., 2015), highlighting the importance of H3K36me3-PWWP interaction for *de novo* methylation. However, DNMT3A, different to DNMT3B, could interact with both di- and tri-methylated state of histone H3K36, and shows a higher binding affinity towards H3K36me2 (Weinberg et al., 2019). H3K36me2 is distributed at both intergenic regions and gene bodies, and is catalyzed by two NSD histone methyltransferase family

enzymes, such as NSD1 and NSD2 (Kuo et al., 2011). Genome wide analysis demonstrated that DNMT3A is targeted to intergenic regions through DNMT3A-H3K36me2 interaction, which can be mistargeted to H3K36me3 modified gene bodies in cells depleted of *Nsd1* and *Nsd2* (Weinberg et al., 2019). Thus, the PWWP domains of DNMT3A and DNMT3B recognize different methylation state of H3K36 and target these enzymes for methylation at different chromatin regions.

Relationship between H3K27me3 and DNA methylation

Mammalian H3K27me3 modification is catalyzed by Polycomb repressive complex 2 (PRC2) (Margueron and Reinberg, 2011). H3K27me3 is almost exclusively associated with CGI regions, which is generally hypomethylated in embryonic stem cells (ESCs) (Cooper et al., 1983; Bird et al., 1985; Ku et al., 2008), indicating the mutually exclusive distribution of H3K27me3 and DNA methylation in ESCs. This might be partially explained by the dependency of DNA methylation on H3K36me2/3, and the antagonizing distribution pattern of H3K36 and H3K27 methylation (Papp and Müller, 2006; Schmitges et al., 2011; Yuan et al., 2011; Gaydos et al., 2012; Popovic et al., 2014; Lu et al., 2016; Huang and Zhu, 2018). Further studies focused on the PRC2 accessory proteins uncovered a more direct molecular mechanism underlying the mutually exclusive distribution of H3K27me3 and DNA methylation. PRC2 accessory proteins, such as PHF1, MTF2, JARID2, AEBP2 and PHF19, are likely involved in the recruitment and/or regulation of enzymatic activity of PRC2 (Cao et al., 2008; Boulay et al., 2011; Casanova et al., 2011; Ballaré et al., 2012; Brien et al., 2012; Hunkapiller et al., 2012; Oksuz et al., 2018; Youmans et al., 2018; Højfeldt et al., 2019). Structural analysis identified the N-terminus of PHF1 and MTF2 bind to unmethylated CpG motif (Li et al., 2017), highlighting a potential mechanism for the restrictive recruitment of PRC2 to these unmethylated regions. In addition, PRC2 was also functionally associated with TET1 enzyme (Neri et al., 2013). Collectively, these studies uncovered the mutually exclusive distribution of H3K27me3 and DNA methylation, and the underlying potential molecular mechanisms. However, H3K27me3 and DNA methylation do overlap at some genomic regions in certain somatic and cancer cells (Brinkman et al., 2012; Statham et al., 2012). During differentiation and carcinogenesis, H3K27me3-silenced gene promoters contain DNA methylation in some sites (Ohm et al., 2007; Schlesinger et al., 2007; Mohn et al., 2008; Rose and Klose, 2014; Chen et al., 2019; Sendžikaitė et al., 2019). Moreover, it has been shown that during early phase of X-chromosome inactivation, expression of *Xist* RNA recruits Polycomb complex for gene silencing. Subsequently, the H3K27me3 silencing mechanism is switched to promoter DNA methylation for long term silencing (Augui et al., 2011; Jégu et al., 2017; Galupa and Heard, 2018). However, the inactivated X-chromosome exhibits a global DNA hypomethylated state due to transcription silencing and reduced H3K36 methylation. Therefore, the relationship and transition between DNA and H3K27 methylation are complicated, which requires further mechanistic studies.

Crosstalk between H3K9me2/3 and DNA methylation

There is a direct cross talk between H3K9 methylation and DNA methylation. H3K9 methylation is required for all DNA methylation in *Neurospora crassa* (Tamaru and Selker, 2001; Tamaru et al., 2003). In *Arabidopsis thaliana* CpNpG methylation is also dependent on H3K9 methylation (Jackson et al., 2002). Albeit lack of a strict link between H3K9me and DNA methylation deposition in mammals, these two repressive modifications are co-localized at heterochromatin regions. Early studies proposed that DNMT3A/3B could deposit DNA methylation through binding to heterochromatin protein 1 (HP1) that recognizes H3K9me3 (Lehnertz et al., 2003). Further, several studies describe direct interactions between DNMT3A/3B and the H3K9 methyltransferases, such as SUV39H1 (Fuks et al., 2003), SETDB1 (Li et al., 2006) and G9a/GLP (Epsztejn-Litman et al., 2008; Chang et al., 2011). However, the functional significance of these interactions to promote DNA methylation has not yet been fully studied.

Compared with *de novo* DNA methylation, DNA methylation maintenance mediated by DNMT1-UHRF1 machinery shows a closer connection with H3K9me2/3 modification. As mentioned above, the TTD and PHD domains of UHRF1 cooperatively bind to H3K9me2/3 modification and show a preference on trimethylated state of H3K9 (Figure 6A) (Hashimoto et al., 2009; Rottach et al., 2010). Due to the technical limitations of knockdown and overexpression experiments, TTD was thought to be essential for UHRF1 chromatin targeting and DNA methylation maintenance in early studies (Rothbart et al., 2012; Rothbart et al., 2013). However, genome edited homozygous TTD mutant mice only shows about 10% reduction of DNA methylation in various tissues tested (Zhao et al., 2016), indicating limited role of TTD for DNA methylation maintenance. These works all focused on the readout of global methylation level, but little is known about the contribution of TTD in the kinetics of DNA methylation maintenance. Recent kinetic analysis demonstrated that TTD and H3K9me2/3 are important for replication-uncoupled DNA methylation maintenance (Ming et al., 2021a). Besides, RFTS domain of DNMT1 could directly recognize H3K9me3 and facilitate DNA methylation maintenance (Ren et al., 2020). DNMT1 was also reported to directly interact with G9a to promote its maintenance efficiency during replication (Estève et al., 2006). Together, these studies highlight the importance of direct crosstalk between H3K9 methylation and DNA methylation.

H3 ubiquitination facilitates the recruitment and activation of DNMT1

Detailed molecular mechanisms of the UHRF1-DNMT1 maintenance apparatus in DNA methylation inheritance were carefully illustrated until recent years. Histone H3 was identified as a ubiquitination target of UHRF1 using *Xenopus* egg extracts (Nishiyama et al., 2013); and both the PHD and RING domains are important for efficient ubiquitination of H3 (Qin et al., 2015). Mass spectrometry analysis identified that H3 could be ubiquitinated at Lys14 (Ishiyama et al., 2017), Lys18 (Qin et al., 2015; Ishiyama et al., 2017) and Lys23 (Nishiyama et al., 2013; Ishiyama et al., 2017), and these ubiquitinated sites could be recognized by the ubiquitin interacting motif (UIM) of RFTS domain in DNMT1 protein (Qin et al., 2015). Crystal structure identified a novel recognition mode of RFTS which simultaneously binds to double ubiquitinated H3 at K18 and K23 (Ishiyama et al., 2017). It was also reported that RFTS domain mediates the homodimerization (Fellinger et al., 2009) and autoinhibition (Syeda et al., 2011; Takeshita et al., 2011) of DNMT1. Strikingly, DNMT1 opens its active site upon binding to H3K18ub/K23ub by the RFTS domain, indicating that ubiquitinated histone by the UHRF1 could allosterically activate the activity of DNMT1. Therefore, these works together demonstrated the essential role of the ubiquitin-binding module of DNMT1 in DNA methylation maintenance (Ishiyama et al., 2017).

A role of H4K20 methylation in recruiting DNMT1 to LINE-1 region

Generally, DNA methylation, H3K9me3 and H4K20me3 coexist at many heterochromatin regions. These repressive marks function cooperatively to silence repetitive DNA sequences in mammalian genomes. Compared with the well-known connections between DNA methylation and H3K9me3, the crosstalk between DNA methylation and H4K20me3 is less reported. Disturbance of DNA methylation and H4K20me3 frequently occurs in cancer cells (Feinberg and Vogelstein, 1983; Eden et al., 2003; Fraga et al., 2005). Reactivation of repetitive elements, especially long interspersed nuclear element-1 (LINE-1), is tightly associated with genome rearrangements in cancers (Rodriguez-Martin et al., 2020), highlighting the importance of the repression of repetitive LINE-1. DNMT1 contains two bromo-adjacent homology (BAH) domains (Yarychkivska et al., 2018), which have been recently shown to specifically recognize methylated H4K20 with a preference for H4K20me3 (Ren et al., 2021). Furthermore, H4K20me3 bound to BAH1 domain could induce an allosteric stimulation of DNMT1 activity (Ren et al., 2021), and the BAH1-H4K20me3 binding module facilitates DNA methylation maintenance especially for the LINE-1 elements (Ren et al., 2021). This work provides a direct crosstalk between DNA methylation and H4K20me3. Thus, RFTS and BAH1 domains of DNMT1 bind to H3ub/H3K9me3 and H4K20me3, respectively, highlighting multivalent communications among repressive marks and DNA methylation maintenance. Nevertheless, it remains unclear whether the *de novo* activity of DNMT1 participates in DNA methylation at LINE-1 regions. Furthermore, novel crosstalk between histone modifications and different domains of DNMTs warrants further investigation.

Roles of DNA methylation in transcriptional memory

Epigenetic memory of gene transcription was described as a heritable change in gene expression or behavior that is induced by an experienced stimulus (D'Urso and Brickner, 2014). Epigenetic memory could be set up and maintained by various epigenetic players, including DNA methylation, histone modifications, histone variants and chromatin remodelers. Epigenetic memory can be divided into cellular transcriptional memory and transgenerational memory based on the time scales of memory maintained. Cellular transcriptional memory refers to the mitotically heritable transcriptional state in response to development cues or environmental stimuli, while the transgenerational memory describes meiotically heritable transcriptional profile generated by experiences of previous generations (D'Urso and Brickner, 2014). Adaptive immunity, chronic inflammation, and neuronal memory are ideally suitable contexts for studying the molecular mechanisms underlying the establishment and maintenance of transcriptional memory.

Transcriptional memory allows certain genes to respond more rapidly and robustly toward previously experienced signals (Bergink et al., 1973). During past years, transcriptional memory of the inducible inositol-1-phosphate synthase (*INO1*) and galactokinase (*GAL*) genes in *Saccharomyces cerevisiae* system are thoroughly studied. It has been shown that several factors/players including nuclear periphery retention, intragenic looping, H2A.Z variant deposition, H3K4 methylation and chromatin remodeler SWI/SNF are important for transcriptional memory. In addition to histone related players, transcriptional memory of *Tat* gene upon glucocorticoid induction is associated with DNA demethylation event (Thomassin et al., 2001), and similar demethylation was also reported at *IL2* gene locus after T cell activation (Murayama et al., 2006). These studies imply the biological significance of DNA demethylation on transcriptional memory establishment and maintenance. Recent published works further demonstrated the importance of DNA methylation in transcriptional memory regulation. Although short-term treatment of tumor necrosis factor α (TNF-α) could activate DNA methylation silenced *IL32* gene

without demethylation step, prolonged TNF-α treatment induces DNA demethylation at both the promoter and CGI region of *IL32* gene which depends on TET and p65 (Zhao et al., 2019). Strikingly, demethylation-induced transcriptional activation of *IL32* persists for a long time after withdrawing of TNF-α (Zhao et al., 2019). Moreover, sustained TNF-α administration uncovers a transcriptional memory induced by the key proinflammatory cytokine TNF-α (Zhao et al., 2020b). *CALCB* gene, the key therapeutic target gene in migraine, shows the strongest transcriptional memory and relies on the active demethylation mediated by TET enzymes (Zhao et al., 2020b). These results suggest that inflammatory signals and memory consolidation might play a role in the development of chronic migraine. Collectively, these works demonstrated that transcriptional memory provoked by TNF-α is governed by active DNA demethylation by TET enzymes. The hypomethylated state of memory gene and related regulatory region might facilitate the chromatin binding of subsequent methylation-sensitive transcription factors, which in turn provoke rapid and robust transcription activation in the subsequent encounter of inflammatory stimuli. Notably, it is intriguing whether DNA demethylation mediated transcriptional memory towards certain environmental and cellular stimuli might also be involved in the development of adaptive immunity malfunction, chronic inflammation, aging and cancer.

Functional impact of epigenetic inheritance

Factors discussed above involved in epigenetic inheritance are important to maintain chromatin states and cell identity. Therefore, it is easy to envision the critical roles of epigenetic inheritance in cell identity during normal development, in disease evolution and in response to environmental stress/cues. In reality, it is challenging to directly link a malfunction in epigenetic inheritance to the occurrence of a particular phenotypes/disease at organism levels. Below, we outline several examples in which alterations of factors involved in epigenetic inheritance contribute to developmental defects and cancers.

Defects in genomic imprinting

A couple of well-studied examples linking defects in epigenetic inheritance to human diseases are the Prader-Willi syndrome (PWS) and Angelman syndrome (AS). PWS and AS are distinct human neurological disorders resulting from defects in genomic imprinting of a gene cluster at 15q11q13 locus. While some genes are only expressed from the maternal allele, several genes including *SNRPN* and *SnoRNA* are expressed paternally, with the maternal allele silenced through DNA methylation. PWS is caused by the loss of the expression of paternally expressed genes, whereas AS is caused by loss of expression of maternally expressed genes. It is estimated that 86% patients with PWS and 92% patients with AS are caused by epimutations without changes at underlying DNA sequence. Of note, about one third of these AS patients show somatic mosaicism in which cells with imprinting defects and normal cells co-exist (Horsthemke and Buiting, 2008). These results indicate that a majority of PWS and AS cases are caused by sporadic errors during the process of establishment, and maintenance of this imprinting locus. Future studies are needed to understand the molecular basis for the generation of epimutations at this imprinted gene cluster.

With the advancement of sequencing-based technologies, more and more imprinted genes have been identified. Currently, it is estimated that over 220 genes are imprinted in human genome (Horsthemke and Buiting, 2008). Moreover, in addition to DNA methylation based on mechanism of genomic imprinting, H3K27me3 alone can also imprint genes during mouse early development (Inoue et al., 2017a; Inoue et al., 2017b). These advancements will likely provide additional insights into how alterations in imprinting contribute to human diseases. For more information about genomic imprinting, we direct readers to two recent reviews on this topic (Peters, 2014; Monk et al., 2019).

A critical role for CAF-1 in maintaining chromatin states and cell identity during development and tumorigenesis

CAF-1, the first identified histone chaperone involved in deposition of new H3-H4 onto replicating DNA, plays an important role in maintaining chromatin states from yeast to human. An early study in *Arabidopsis* found that CAF-1 is important to maintain cellular and functional organization of both shoot apical meristem and the root apical meristem (Kaya et al., 2001), which are responsible for postembryonic development of plant architecture. Recently, it has been shown that depletion of CAF-1 in mouse ES cells results in an increase in 2C-like cells (Ishiuchi et al., 2015). Furthermore, depletion of CAF-1 in mouse embryonic fibroblast increases in the reprograming efficiency of these cells into iPSC, likely due to an increase in chromatin accessibility (Cheloufi et al., 2015). Therefore, CAF-1 is important to maintain chromatin states and cell identity likely in all cell types during normal development.

Two recent studies also report that alterations in CAF-1 expression can promote tumorigenesis and drive tumor metastasis. It is known for a long time that CHAF1B, a subunit of CAF-1, is overexpressed in several solid tumors and acute megakaryocytic leukemia (AMKL) (Polo et al., 2010; Sykaras et al., 2021). However, it was not known whether the overexpression of CHAF1B has any role in tumorigenesis. Using mouse models, it has been shown that CAF-1 is essential for normal hematopoiesis. However, overexpression

of CHAF1B interferes with the association of transcription factors such as CEBPA involved in myeloid differentiation, which in turn promotes leukemia. The effects of CHAF1B overexpression on leukemia genesis are linked to the role of CHAF1B in nucleosome assembly of new H3-H4 (Volk et al., 2018). On newly replicating chromatin, transcription factor binding sites are temporarily blocked (Ramachandran and Henikoff, 2016). As parental H3-H4 can memorize their positions along DNA following DNA replication (Escobar et al., 2019), it is likely that the block of transcription factors is caused by the deposition of new H3-H4 by CAF-1. Therefore, overexpression of CHAF1B likely exacerbates the blocking effects of CAF-1, thereby inhibiting myeloid differentiation. In the future, it would be interesting to determine whether CAF-1 overexpression in solid tumors also plays a causal role in tumorigenesis.

While CAF-1 overexpression promotes leukemia, a recent study indicates that reduced CAF-1 expression contributes to tumor metastasis (Gomes et al., 2019). Tumor metastasis, referring to cancer cells migrating from the primary organs through the blood or lymph systems and forming tumors at new organs, contributes to the largest fraction of cancer-induced death (Fares et al., 2020). Genome wide analysis of several tumors and their matched metastatic ones indicate that epigenetic changes, but not genetic mutations, are likely the dominant force in the development of tumor metastasis (McDonald et al., 2017; Chatterjee et al., 2018). Using carcinoma models, it has been shown that metastatic signals suppress the expression of CAF-1, leading to reduced density of canonical histone H3.1/H3.2, which are assembled into nucleosomes by CAF-1. This will trigger an increase in HIRA mediated nucleosome assembly of H3.3 and the acquisition of more aggressive and metastatic characteristics of cancer. Depletion of HIRA suppresses the metastatic phenotypes (Gomes et al., 2019). Together, these studies highlight the dynamic regulation of CAF-1-mediated nucleosome assembly of H3.1/H3.2 and HIRA-mediated nucleosome assembly of H3.3 in changes of cell identity to a more metastatic one. In the future, it would be interesting to determine to what extent other factors involved in epigenetic inheritance discussed above may play in promoting cell fate changes and thereby metastasis.

Summary and future directions

In the last several years, we have witnessed major advances in the understanding of epigenetic inheritance. Specifically, studies from various systems have established that repressive histone modifications can be inherited, at least in part, through the read-and-write mechanism. Because of the dynamic and reversible natures of histone modifications, it is also clear that non-coding RNAs and DNA sequence specific binding proteins are needed to recruit histone modifying enzymes locally for the stable inheritance of a histone modification. More importantly, we have also witnessed major advances in our understanding of the recycling of parental histones, which contain epigenetic modifications, following DNA replication. Finally, we have also begun to appreciate the importance of maintenance of chromatin states and cell identity to prevent diseases including tumors. These advances have laid a solid foundation for dissecting molecular mechanisms of epigenetic inheritance during normal development, and in tumorigenesis. However, many questions still remain to be answered. How is parental histone transfer/recycling regulated? Are there other factors involved in parental histone transfer? Is there any coordination between parental histone transfer and *de novo* deposition of new H3-H4, and if there is, how do these two pathways coordinate to promote nucleosome formation? Considering the extensive cross talk between DNA methylation and histone modifications, do protein machineries involved in the heritance of DNA methylation also contribute to the inheritance of histone modifications, or *vice versa*? Do alterations in epigenetic inheritance contribute to the establishment of alterative chromatin states that specify disease evolution such as the transition of cancer cells to metastatic cells? Future studies to address these and other questions in epigenetic inheritance will advance our understanding of epigenetic inheritance and the contribution of malfunction of this process to human disease.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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