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PERSPECTIVE

Histones, histone chaperones and nucleosome assembly

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ABSTRACT

Chromatin structure governs a number of cellular processes including DNA replication, transcription, and DNA repair. During DNA replication, chromatin structure including the basic repeating unit of chromatin, the nucleosome, is temporarily disrupted, and then reformed immediately after the passage of the replication fork. This coordinated process of nucleosome assembly during DNA replication is termed replication—coupled nucleosome assembly. Disruption of this process can lead to genome instability, a hallmark of cancer cells. Therefore, addressing how replication-coupled nucleosome assembly is regulated has been of great interest. Here, we review the current status of this growing field of interest, highlighting recent advances in understanding the regulation of this important process by the dynamic interplay of histone chaperones and histone modifications.

CHROMATIN STRUCTURE AND NUCLEOSOME ASSEMBLY

In eukaryotic cells, genomic DNA is packaged into chromatin, an organized complex of DNA and proteins (Luger et al., 1997; Kornberg and Lorch, 1999; Wu and Grunstein, 2000; Chodaparambil et al., 2006). The fundamental unit of chromatin is the nucleosome, consisting of 146 base pairs of DNA wrapped around a histone octamer containing a tetramer of histones H3-H4 and two dimers of histones H2A-H2B. During S phase of the cell cycle, chromatin structure must be propagated to daughter cells to maintain gene expression state and genome integrity. How chromatin structure is inherited during S phase of the cell cycle remains largely unknown (Goldberg et al., 2007). During DNA replication, eukaryotic cells disassemble nucleosomes to facilitate progression of the DNA replication machinery (Falbo and Shen, 2006). Following replication, newly-synthesized histones, as well as parental histones, must be deposited onto the nascent DNA strands to mediate nucleosome formation and reassembly of chromatin higher order structure. This coupling of DNA replication and nucleosome assembly is termed replication-coupled (RC) nucleosome assembly. It is believed that DNA RC nucleosome assembly plays an important role in the inheritance of chromatin structure.

During RC nucleosome assembly, parental H3-H4, as well as newly-synthesized H3-H4, are deposited first followed by rapid deposition of H2A-H2B dimers to form nucleosomes. Once assembled into nucleosomes, H3-H4 molecules remain stably bound to DNA, whereas nucleosomal H2A and H2B can exchange with free H2A and H2B (Rocha and Verreault, 2008; Ransom et al., 2010). Therefore, it is important to understand how H3-H4 are deposited, the factors involved in deposition and the regulatory mechanisms contributing toward nucleosome assembly. Because the deposition of newly-synthesized H3-H4 molecules and the regulation of their deposition are relatively well understood compared to the transfer of parental histones H3-H4 behind replication forks, this perspective will focus on how newly-synthesized H3-H4 are deposited.

THE FUNCTION OF THREE HISTONE CHAPERONES IN RC NUCLEOSOME ASSEMBLY IN YEAST

Deposition of newly-synthesized H3-H4 during DNA replication requires histone chaperones. Histone chaperones are a group of proteins that help regulate nucleosome deposition by binding to the positively charged histones and shielding their charge from the highly negatively charged DNA (Tyler, 2002).

The classic histone chaperone involved in RC nucleosome assembly is chromatin assembly factor 1 (CAF-1). CAF-1 consists of three subunits (Kaufman et al., 1997) and was first identified in human cells as a factor that promotes nucleosome assembly during DNA replication (Stillman, 1986). CAF-1 binds H3-H4 and facilitates nucleosome assembly following DNA replication and DNA repair by interacting with PCNA, a component of the DNA replication machinery (Shibahara and Stillman, 1999). Yeast cells lacking CAF-1 exhibit reduced silencing at telomeres, as well as the silent mating type loci, and are sensitive to DNA damaging agents (Kaufman et al., 1997; Linger and Tyler, 2005), phenotypes shared among nucleosome assembly factor mutants.

The ability of CAF-1 to deposit H3-H4 onto replicated DNA is assisted by Asf1, another H3-H4 histone chaperone (Tyler et al., 1999; Mello et al., 2002). Asf1 was first identified in a genetic screen based on its ability to disrupt transcriptional silencing in budding yeast when overexpressed (Le et al., 1997). Later, it was shown that Asf1 was a histone chaperone functioning in both replication-coupled and replication-independent nucleosome assembly (Tyler et al., 1999). Structural studies have revealed that Asf1 binds H3-H4 dimers through an H3 interface that is involved in the formation of $(H3\text{-}H4)_2$ tetramers (English et al., 2006). In human cells, it is proposed that Asf1 can disrupt parental nucleosomes (Groth et al., 2007). Furthermore, Asf1 is required for acetylation of histone H3 lysine 56 (H3K56Ac), a mark of newly-synthesized histones that has been found to be important for DNA replication and DNA repair (Recht et al., 2006; Chen et al., 2008; Li et al., 2008).

A more recently described H3-H4 histone chaperone in yeast is Rtt106. Rtt106 was first identified in a genetic screen for regulators of Ty1 transposition in budding yeast (Scholes et al., 2001). In a separate genetic screen, we identified Rtt106 as a protein that functions in parallel to PCNA in transcriptional silencing (Huang et al., 2005). Furthermore, we have shown that Rtt106 is a histone H3-H4 chaperone involved in RC nucleosome assembly (Li et al., 2008). Like mutations in genes encoding other histone chaperones, the *rtt106*Δ mutant cells exhibit significant loss of silencing at telomeres and at the silent mating type locus and are sensitive to DNA damage agents when combined with deletion of *CAC1*, the large subunit of CAF-1 (Huang et al., 2007; Li et al., 2008). Rtt106 is also proposed to have a role in replication-independent nucleosome assembly as well as the regulation of histone gene expression (Imbeault et al., 2008; Fillingham et al., 2009).

These remarkable discoveries have led to the following question: how are $(H3\text{-}H4)_2$ tetramers, one of the building blocks of nucleosomes, formed during S phase of the cell cycle if Asf1 binds the same H3 surface involved in $(H3\text{-}H4)_2$ tetramer formation? We and others have made observations that support a model in which H3-H4 dimers are transferred from Asf1-H3-H4 to CAF-1 and Rtt106, which in turn deposit H3-H4 onto replicating DNA for nucleosome formation. First, the association of histone H3-H4 with CAF-1 and Rtt106 is reduced in *asf1*Δ cells (Li et al., 2008). Second, Asf1 has been shown to interact directly with CAF-1 (Tyler et al., 2001; Mello et al., 2002). Together, these three histone chaperones, CAF-1, Rtt106 and Asf1, coordinate the deposition of newly-synthesized H3-H4 during DNA replication, but how exactly these chaperones cooperate is unclear (Fig. 1).

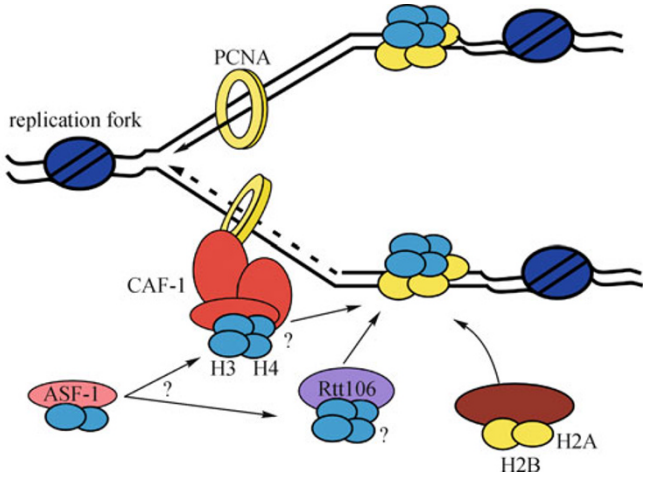

Figure 1. Coordination of histone chaperones for replication-dependent nucleosome assembly. During DNA replication, nucleosomes are disassembled and then reassembled behind the replication fork. The three histone chaperones, CAF-1, Asf1 and Rtt106 coordinate to deposit newly-synthesized H3-H4 onto the replicated DNA. It is still unclear how the Asf1-H3-H4 complex interacts with CAF-1 and Rtt106 for histone deposition. It is also unknown whether CAF-1 and Rtt106 bind H3-H4 dimers or tetramers.

MULTIPLE ACETYLATION EVENTS REGULATE ASSEMBLY OF NEWLY-SYNTHESIZED HISTONES H3 AND H4 IN BUDDING YEAST

Modifications on histones regulate distinct cellular processes, including gene transcription, DNA replication, and DNA repair. These diverse functions are carried out by distinct modifications, including acetylation, phosphorylation, methylation and ubiquitination, which modulate chromatin structure and/or recruit proteins to chromatin to mediate a specific process (Strahl and Allis, 2000; Turner, 2000; Jenuwein and Allis, 2001; Vidanes et al., 2005). Histone acetylation is catalyzed by histone acetyltransferases (HATs), a group of enzymes that transfer the acetyl group from the cofactor acetyl-Coenzyme A (acetyl-CoA) to the ε-amino group of lysine residues on histones (Marmorstein and Roth, 2001; Roth et al., 2001; Carrozza et al., 2003; Marmorstein, 2004). It was discovered years ago that newly-synthesized histones were acetylated and rapidly deacetylated following deposition (Ruiz-Carrillo et al., 1975; Jackson et al., 1976). It is only recently that we have begun to appreciate the function of acetylated newly-synthesized H3-H4.

The most highly-conserved mark of newly-synthesized histones is acetylation of histone H4 lysines 5 and 12 (H4K5, 12Ac). While acetylation on newly-synthesized histone H3 is conserved, the distinct acetylated sites are not. In HeLa cells, acetylation at the H3-N terminus of new H3 is barely detectable (Sobel et al., 1995). Moreover, acetylation of H3 lysine 56, a well-established and abundant mark of newly-synthesized H3 in budding yeast (Masumoto et al., 2005), is less abundant in mammalian cells (Jasencakova et al., 2010). Acetylation of distinct sites of newly-synthesized H3-H4 is catalyzed by different histone acetyltransferases. For instance, Hat1 acetylates lysine 5 and 12 of H4 (Ai and Parthun, 2004). Rtt109 acetylates lysine 56 of H3 in yeast (Driscoll et al., 2007; Han et al., 2007), and in mammalian cells, this modification is catalyzed by CBP/p300 and/or Gcn5 (Das et al., 2009; Tjeertes et al., 2009). Recently, we have shown that new H3 acetylation at the N-terminal tail is carried out by the lysine acetyltransferases Gcn5, Rtt109 and possibly Elp3 (Li et al., 2009; Burgess et al., 2010). Thus, acetylation of multiple sites at newly-synthesized H3-H4 is catalyzed by distinct lysine acetyltransferases (Fig. 2). How acetylation of these sites functions to promote nucleosome assembly is an interesting question.

Genetic studies suggest that acetylation of newly-synthesized H3-H4 is important for nucleosome assembly (Ma et al., 1998). Only recently have studies revealed that histone acetylation serves an important regulatory function during nucleosome assembly. For instance, In yeast cells, H3K56Ac, which peaks during S phase of the cell cycle (Masumoto et al., 2005; Han et al., 2007; Chen et al., 2008), increases the binding affinity between H3-H4 with CAF-1 and Rtt106 and promotes efficient deposition of H3-H4 onto

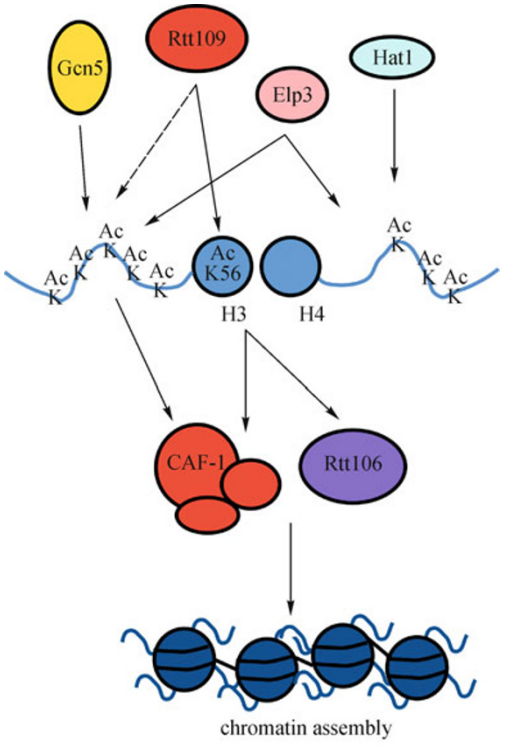

Figure 2. Histone acetylation of H3-H4 regulates replication-dependent nucleosome assembly by promoting the interaction of histones with histone chaperones. The histone acetyltransferases Gcn5, Rtt109, Elp3, and Hat1 are involved in marking newly-synthesized histones H3-H4. Some of these acetylation marks are known to promote histone interactions with histone chaperones for chromatin assembly. Acetylation of the N terminus of H3 is primarily carried out by Gcn5. Elp3 and Rtt109 also contribute to the acetylation of the H3 N terminus, but how these three distinct lysine acetyltransferases coordinate these acetylation events is not known. In addition, Rtt109 acetylates H3K56 on the core of histone H3. Hat1 and Elp3 acetylate lysine 5, 8 and 12 on H4; however, the functions of these H4 marks are unclear.

replicating DNA by these two histone chaperones (Li et al., 2008). In contrast, acetylation of lysine residues at the H3 N-terminus regulates the binding of H3-H4 with CAF-1, but not Rtt106 (Burgess et al., 2010). Therefore, acetylation of H3 lysine 56 and acetylation of lysine residues at the H3 N-terminus function to promote nucleosome assembly by enhancing histone binding with distinct histone chaperones.

Finally, despite the conservation of H4K5, 12Ac from yeast to humans, its function is still unknown. In mammalian cells, prior to deposition, the canonical H3, H3.1, is associated with H4K5,12Ac, which is distinct from the pattern observed on nucleosomal H3.1-H4 (Loyola et al., 2006). Histone H4 molecules in CAF-1-H3-H4 complexes are acetylated at lysine residues 5, 8 and 12 in both yeast and human cells (Verreault et al., 1996; Zhou et al., 2006). Furthermore, the

diacetylated H4 pattern is also found on H3.1-H4 dimers associated with Asf1 (Jasencakova et al., 2010). Therefore, it is tempting to speculate that H4K5, 12Ac also regulates the interaction between H3-H4 with histone chaperones. Alternatively, acetylation of these lysine residues may facilitate nuclear import of newly-synthesized H3-H4. In yeast, Hat1, the enzyme catalyzing H4K5, 12Ac, associates with newly-synthesized H3-H4 within the cytoplasm and remains associated as the entire complex moves to the nucleus before transferring the associated histones to other histone chaperones (Ai and Parthun, 2004; Shahbazian and Grunstein, 2007). Future studies are needed to address these possibilities.

PERSPECTIVE: THE FUNCTION OF MODIFICATIONS ON NEWLY-SYNTHESIZED HISTONES IN NUCLEOSOME ASSEMBLY IN MAMMALIAN CELLS

Many of the studies on nucleosome assembly and its regulation cited above have been carried out in budding yeast. While many of the RC nucleosome assembly components are conserved from yeast to mammalian cells, nucleosome assembly and its regulation have their own distinct characteristics in mammalian cells. First, in mammalian cells, there are two sequence homologs of Asf1, Asf1a and Asf1b. Like Asf1 in yeast, both Asf1a and Asf1b regulate replication-dependent and replication-independent nucleosome assembly; however, Asf1a and Asf1b appear to have distinct functions. For example, Asf1a, but not Asf1b, interacts with HIRA, a H3-H4 chaperone involved in replication-independent nucleosome assembly (Tagami et al., 2004). Second, to date, there is no clear mammalian homolog of the yeast Rtt106; however, recent studies suggest that the H3.3-H4 histone chaperone DAAX and FACT complex contain regions similar to the yeast Rtt106 (VanDemark et al., 2006; Li et al., 2008; Drane et al., 2010). Third, while H3K56Ac, catalyzed by CBP/P300 and/or Gcn5 (Das et al., 2009; Tjeertes et al., 2009), has been shown to have similar functions in mammalian cells as yeast (Das et al., 2009) (Yuan et al., 2009), it is still unclear as to how this modification regulates nucleosome assembly in mammalian cells, as its abundance is relatively low compared to yeast cells (Jasencakova et al., 2010). Fourth, there are two major forms of H3 in mammalian cells, canonical H3 (H3.1, H3.2) and histone H3 variant H3.3, which are deposited by distinct histone chaperones (Ahmad and Henikoff, 2002). Finally, while modifications on newly-synthesized H3-H4 have been extensively profiled in mammalian cells (Loyola et al., 2006; Jasencakova et al., 2010), the functions of these modifications have not been well studied. Therefore, it would be interesting to determine how modifications on newly-synthesized H3-H4 regulate nucleosome assembly pathways in mammalian cells and how this regulation coordinates with concurrent DNA replication.

In summary, over the past few years, we have gained great insight into the regulation of nucleosome assembly through histone modifications and control of histone-histone chaperone interactions. However, there are still many unanswered questions. How does the chromatin modifying machinery aid in the regulation of nucleosome assembly and what regulates these interactions? How does the Asf1-H3-H4 complex pass histone dimers to CAF-1 and/or Rtt106 for deposition? How are parental nucleosomes transferred behind the DNA replication fork? What contributes to histone chaperone specificity for particular H3 variants? Do modifications on H2A-H2B facilitate their deposition at the replication fork?

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