SCIENCE CHINA
Life Sciences

SPECIAL TOPIC
• REVIEW •

January 2012 Vol.55 No.1: 15–19
doi: 10.1007/s11427-012-4269-z

Roles of chromatin assembly factor 1 in the epigenetic control of chromatin plasticity

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Received July 7, 2011; accepted July 30, 2011

Genetic information embedded in DNA sequence and the epigenetic information marked by modifications on DNA and histones are essential for the life of eukaryotes. Cells have evolved mechanisms of DNA duplication and chromatin restoration to ensure the inheritance of genetic and epigenetic information during cell division and development. In this review, we focus on the maintenance of epigenetic landscape during chromatin dynamics which requires the orchestration of histones and their chaperones. We discuss how epigenetic marks are re-established in the assembly of new chromatin after DNA replication and repair, highlighting the roles of CAF-1 in the process of changing chromatin state. The functions of CAF-1 provide a link between chromatin assembly and epigenetic restoration.

CAF-1, epigenetic information, chromatin plasticity, signal transduction, histone chaperone

Citation: Huang H, Jiao R J. Roles of chromatin assembly factor 1 in the epigenetic control of chromatin plasticity. Sci China Life Sci, 2012, 55: 15−19, doi: 10.1007/s11427-012-4269-z

In eukaryotic cells, DNA is packed into nucleosome units, the core particle of which is a hetero-octamer that is composed of histone proteins (H2A, H2B, H3 and H4) with 147 base pairs of DNA wrapped around [1,2]. Nucleosomal arrays are connected by linker DNA and linker histone H1 and organized to form the 30 nm chromatin fiber, which serves as the template for gene expression and genetic inheritance [3–8]. In addition to the genetic information that is embedded in the DNA, gene expression and developmental pattern formation are largely regulated by histone modifications that encode the epigenetic information. Both genetic and epigenetic information must be faithfully preserved after DNA replication and repair for normal life cycles. The processes of DNA replication and repair involve assembly and disassembly of the chromatin, both of which require participation of chromatin chaperones that regulate interactions between the negatively charged DNA and the positively charged histones, so as to maintain proper chromatin structure. A number of chaperones and chromatin remodelers have been identified to act in repair- and replication-coupled chromatin assembly/disassembly [9–11].

Chromatin assembly factor 1 (CAF-1) is one of the histone chaperones mediating chromatin assembly after DNA replication and repair [12–14]. This three-subunit protein complex was first purified from the nuclei of human cells about 20 years ago, whose capability of depositing histones H3-H4 to newly synthesized DNA was characterized by *in vitro* experiments [12,13]. Since then, extensive studies in different species focusing on the *in vivo* functions of CAF-1 have demonstrated that CAF-1 is an evolutionarily conserved complex in the processes of DNA replication and repair [11,15–19]. Given its crucial role in nucleosome assembly/disassembly, understanding of how CAF-1 functions in eukaryotic cells has emerged to provide a unique window of opportunity to understand the chromatin dynamics. This review will focus on the interplay among the roles

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of CAF-1 in maintaining genomic and epigenetic stability, in an effort to unveil the mechanisms of dual information preservation during cell division and development.

1 Nucleosome assembly during DNA replication

DNA replication-coupled nucleosome assembly is a sequential process. The histones H3 and H4 are first loaded on newly synthesized DNA as a heterodimer, followed by deposition of another heterodimeric histones of H2A and H2B [20–23]. CAF-1 is required for the first step, targeting histones H3 and H4 onto the DNA [14,24]. The acetylation pattern of newly synthesized histones H3 and H4 is important marks for CAF-1 recognition [25–28]. CAF-1 recognizes H4K5, H4K12 and H3K56 acetylation [26,29]. The discriminative efficiency of histone deposition by CAF-1 onto replicated and un-replicated DNA suggests that CAF-1 mediated nucleosome assembly is a replication-dependent process [24]. The interaction of CAF-1 with the proliferating cell nuclear antigen (PCNA) via its largest subunit underlies the molecular basis of the preference for CAF-1 to deposit histones onto newly synthesized DNA [13,30]. Anti-silencing factor 1 (ASF1) is another member of histone deposition pathway. It was purified in a complex with acetylated histones H3 and H4, which promotes nucleosome assembly activity of CAF-1 *in vitro* [31,32]. The *in vivo* functional synergy between CAF-1 and ASF1 is consistent with the *in vitro* data [9,15,33]. CAF-1, in association PCNA, connects DNA duplication to nucleosome assembly, which raises the possibility that CAF-1 may couple the epigenetic inheritance to DNA replication.

2 Duplication of epigenetic information of heterochromatin

Specific modifications on histone tails are crucial for heterochromatin identity. The intrinsic mechanism(s) that ensures the faithful inheritance of epigenetic information may rely on histone H3-H4 heterodimer partitioning [34]. The silent signatures of heterochromatin are associated with histone variant H3.1, whereas H3.3 marks actively-transcribed euchromatin [35–37]. The intactness of H3.1-H4 dimer facilitates the new histone to copy the modifications from its neighboring parental H3.1-H4 dimer in the same nucleosome. On the other hand, a significant amount of H3.3-H4 dimers keep on splitting during replication-dependent deposition [34]. However, the splitting event is likely a region-specific but not variant specific, because the H3.1-H4 dimer becomes splitting when it is within the euchromatin territory [34,38]. CAF-1 is the chaperone required for replication-dependent loading of H3.1 [39,40]. Heterochromatin abnormality and impairment of heterochromatic hallmarks such as H3K9 methylation and HP1 association in CAF-1 defective cells have been reported in various cellular and developmental contexts [15,41–43]. A plausible explanation could be that a deficit of CAF-1 impairs the proper incorporation of H3.1, and thus interrupts the modification pattern and heterochromatin organization. However, this interpretation is opposed by two pieces of previous evidence. First, H3.3 can bear similar modifications to that of H3.1 if it is loaded in the vicinity of H3.1 region [38]. Second, loss of heterochromatic modification pattern in CAF-1 depleted-cells is not a replication-dependent event [42,43]. Another assumption that the load of heterochromatin protein 1 (HP1) with the assistance of CAF-1 is critical for heterochromatin organization is more likely the reality. HP1 is an integral component of heterochromatin [44,45]. The physical interaction between HP1 and CAF-1 suggests a mutual recruitment to properly deliver HP1 to the prospective heterochromatin region [39,43,46]. Currently, it remains unknown, but worthy to be investigated, whether there is functional connection between HP1-CAF-1 complex and H3.1-CAF-1 complex, given the notion that no HP1 is present in the H3.1-CAF-1 complex [39]. What determines the prospective heterochromatin region remains a question.

HP1 is responsible for the silencing state of pericentric heterochromatin, while polycomb group (PcG) of proteins is required for the intercalary heterochromatin pattern. In addition to its association with HP1, CAF-1 also interacts with PcG proteins, which suggests an important role for CAF-1 in maintaining PcG-mediated homeotic gene silencing [15,47]. The p55 subunit of CAF-1 complex is important for histone H3K27 tri-methylation, which is a hallmark of PcG-mediated gene silencing [47]. The participation of CAF-1 in both HP1-mediated and PcG-related epigenetic memory suggests a pivotal role of CAF-1 in the epigenetic plasticity of chromatin organization.

3 Re-establishment of chromatin after DNA repair

The expression of CAF-1 is induced when cells encounter DNA damages [48]. Abrogation of either of Cac1, Cac2 or Cac3, components of the yeast CAF-1, leads to hypersensitivity of the cells to UV irradiation [18]. Furthermore, depletion of CAF-1 causes defects in double-strand break (DSB) repair, indicating an important function of CAF-1 in DNA repair [15,48]. CAF-1-dependent incorporation of histone H3.1 occurs at repair sites [49]. This process occurs outside of the S phase although both H3.1 and CAF-1 are suggested to be replication-dependent [49]. It remains an open question how the epigenetic memory is re-established when new histones are incorporated at the repaired sites of the chromatin. One possible mechanism that resembles the semi-conservative replication-coupled chromatin assembly as described in the previous section could account for the

maintenance of epigenetic information after DNA repair. The H3.1-H4 dimer that did not split during DNA repair serves as the epigenetic template for newly deposited histones. CAF-1 functions to incorporate the new histones following DNA repair and promote the epigenetic memory re-establishment at DNA repair sites. Special modifications on the incorporated histones, such as acetylation of H3K56, are required for CAF-1 recognition and for promoting the process of chromatin reassembly [29,50,51].

In addition to the function in new histone deposition, CAF-1 also recruits HP1 to chromatin in response to DNA damages. HP1 plays various roles in transcription, replication and chromatin organization [52–55]. Recent studies show that HP1 acts as one of the pivotal factors for DNA repair as well [56]. The molecular basis for targeting and loading HP1 to the damaged sites by CAF-1 lies in the interaction between PXVXL motif of CAF-1-p150 and the chromoshadow domain of HP1 [57]. Depletion of either CAF-1 or HP1 leads to defects in Rad51 loading and BRCA1 recruitment, suggesting that the interaction between CAF-1 and HP1 is essential for homologous recombination (HR)-mediated DNA repair [57]. The HP1 accumulation at damage sites is a transient event unless the damage occurs in the specific region that is marked by H3K9me3 [57]. The tightly controlled timing of HP1 retention suggests that CAF-1 is required for the loading but not maintaining of HP1 at the chromatin sites. The maintenance of HP1 on chromatin is likely regulated by histone modifications, such as H3K9me3.

The next question is what delivers or recruits CAF-1. PCNA is a possible candidate, which is the platform for CAF-1 in replication-dependent chromatin assembly [13]. Other DNA repair factors that interact with CAF-1, such as BLM and WRN, could also play important roles, at least in part, in delivering CAF-1 [58,59]. The PCNA-CAF-1 interaction occurs upon the presence of DNA damages [60]. However, it remains to be elucidated whether this interaction is required for histone incorporation and/or HP1 recruitment. It is likely that CAF-1 plays a dual role in the process of DNA repair, either sequentially or simultaneously. One is that CAF-1 recruits HP1 to the damage sites, which is an essential early event of DNA damage response. The other is that CAF-1 delivers histones to the DNA damage sites and functions to keep the integrity of histone modifications after DNA repair. In summary, CAF-1 coordinates the action of HP1 which functions to reorganize chromatin to promote DNA repair progression and the behavior of histone deposition to facilitate chromatin restoration, which underscores the critical roles of CAF-1 in the maintenance of both genomic and epigenetic stability.

4 Timing and progression of S phase in the cell cycle

During S phase of the cell cycle, not only DNA is duplicated, but also replicated daughter DNAs have to be compacted into distinct highly ordered chromatin domains with special architecture. Therefore, the timing of DNA replication and the decoration of chromatin are the determinants of the length of S phase. While euchromatin is replicated throughout the S phase, heterochromatin seems to be the late replication [61]. The achievement of high-order heterochromatin domain requires the displacement and association of HP1 protein. The complexity of heterochromatin decorations can prolong the progression of the S phase [62]. Because CAF-1 is one of the key players in chromatin assembly and HP1 association, it is attractive to consider CAF-1 as one of the indispensible factors for S phase progression. It has been reported that depletion of CAF-1-p150, but not p60 reduces late S phase population of cells [63]. The interaction between CAF-1 and HP1 through the p150 subunit is required for pericentric heterochromatin replication as well as S phase progression. Since the length of S phase is adjustable during, for instance, *Drosophila* early embryo development [62], CAF-1 may be an integral factor regulating the timing of S phase during development. It would be interesting to determine whether this function of CAF-1 is dependent on or independent of its histone deposition activity.

5 Fine-tune of the chromatin contexts for signaling

Signaling pathways often exert their final effects through transcriptional regulation, the action of which is dependent on the local chromatin contexts of the target genes of a particular pathway. Condensed chromatin organization renders that transcription machinery is inaccessible to the gene regulatory region, while relaxed chromatin is appropriate for gene activation. Thus, the output of a signaling pathway is eventually regulated by nucleosome positioning and chromatin remodeling, which is mediated by either histone modifications or the action of chromatin chaperones and/or chromatin remodelers [64–66]. It has been reported that chromatin chaperone Asf1 suppresses Notch pathway via interacting with Su(H) and the co-repressor Hairless, whereas another histone chaperone NAP1 modulates Notch silencing by regulating both histone H3 deacetylation and demethylation [67,68]. Nucleosome remodeling factor NURF has been shown to be involved in various signaling pathways including Ecdysone, Wingless and Notch [69–72]. The compacted chromatin structure accomplished by CAF-1 seems to be unsuitable for gene expression activation. In this regard, an upregulation of the target genes of a particular signaling pathway is expected to be observed upon CAF-1 depletion. Unexpectedly, CAF-1 is reported to be involved in transcriptional activation [73]. Our microarray results support the idea of an overall compromised transcription in CAF-1 defective cells (unpublished data). It remains elusive to connect CAF-1 to specific signaling

pathways.

6 Perspectives

The biological processes including replication, repair and transcription are accompanied by assembling and disassembling of chromatin in order to gain accessibility to DNA, to maintain and to restore genetic and epigenetic features of the genome in eukaryotic cells. In this review, the possibility for CAF-1 to be involved in these events is discussed, aiming to delineate the mechanism(s) of genetic and epigenetic maintenance. Although over 20 years of study have advanced much of our understanding of CAF-1 function, there are still questions remained to be resolved as described in the previous sections. For example, is the interaction between CAF-1 and PCNA required for the histone incorporation and HP1 recruitment after DNA repair? Is CAF-1 involved in chromatin dissembling? Given that the integrity of H3.1-H4 dimer preserves the epigenetic information on histones H3 and H4, is the inheritance of modifications on H2A-H2B related to the control of epigenetic inheritance for H3-H4?

Scientific progress relies largely on the innovation of research techniques. The reconstituted artificial chromatin *in vitro* provides an effective system to evaluate the contribution of histone chaperones in the process of chromatin assembly/disassembly [74]. The characteristics of transcriptional activation are successfully recapitulated with this simplified chromatin system. Thus, it is plausible to artificially turn on/off the replication and repair processes in this system as well. Besides, other device such as development of feasible live imaging techniques for CAF-1 will be much useful for final resolution of CAF-1's functions in maintaining genetic and epigenetic information during cell division and development.

This work was supported by the National Natural Science Foundation of China (Grant No. 31071087) and National Basic Research Program of China (Grant No. 2009CB918702).

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