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Histone H3 K56 acetylation, chromatin assembly, and the DNA damage checkpoint

*Jessica A. Downs**

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ABSTRACT

The role of chromatin and its modulation during DNA repair has become increasingly understood in recent years. A number of histone modifications that contribute towards the cellular response to DNA damage have been identified, including the acetylation of histone H3 at lysine 56. H3 K56 acetylation occurs normally during S phase, but persists in the presence of DNA damage. In the absence of this modification, cellular survival following DNA damage is impaired. Two recent reports provide additional insights into how H3 K56 acetylation functions in DNA damage responses. In particular, this modification appears to be important for both normal replication-coupled nucleosome assembly as well as nucleosome assembly at sites of DNA damage following repair.

1. Introduction

DNA in eukaryotes is packaged into chromatin *in vivo* primarily by association with histone proteins. The nucleosome is the basic unit of chromatin and comprises two left handed superhelical turns of DNA wrapped around an octamer of two copies of each of the four core histones; H3, H4, H2A and H2B [1]. Beyond this basic level of compaction, chromatin can form into a number of higher order structures. These structures are generally inhibitory to processes requiring access to the DNA, such as transcription, replication and repair. Not surprisingly, therefore, there are a plethora of enzymatic activities in the cell that can modulate chromatin structure. These broadly fall into two categories: ATP-dependent chromatin remodelling enzymes and covalent modification of histones.

When DNA damage occurs, the recognition and repair of the lesion must occur within the context of chromatin. Both ATP-dependent chromatin remodelling activities and histone modifications have been implicated in the cellular response to DNA damage (for review, see [2]).

Histone H3 K56 was found to be acetylated when histones from budding yeast were analyzed by mass spectrometry [3,4]. Strains lacking an acetylatable lysine at this position were found to be sensitive to a subset of genotoxic agents that cause replicative stress, such as camptothecin (CPT [3]). The residue is globally acetylated during S phase, but disappears rapidly in G2. However, acetylation persists when cells are treated with CPT, and, importantly, when sites of CPT-induced breaks were purified, this modification was present, demonstrating that it persists at sites of damage [3].

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Subsequent work identified the major histone acetyltransferase responsible for K56 acetylation as Rtt109 [5,6], which works together with the histone chaperone Vps75 [5]. Deacetylation is dependent on the NAD-dependent deacetylases Hst3 and Hst4 [7]. Strains lacking either Rtt109 or Hst3/Hst4 are hypersensitive to genotoxic agents, have increased levels of spontaneous DNA damage and exhibit synthetic phenotypes with strains lacking genes involved in DNA repair and replication (see [8] and refs therein). Together, these data suggest that the appropriate acetylation and deacetylation of H3 K56 during S phase is critical for genome stability. Two recent reports provide insights into the mechanism by which H3 K56 acetylation functions to mediate chromatin assembly [9,10].

2. Chromatin assembly

Newly synthesized H3 and H4 are assembled into nucleosomes with the help of the CAF-1 chromatin assembly factor [11]. It is well established that the N-terminal tails of H3 and H4 are acetylated prior to chromatin incorporation, and this is important for assembly *in vivo* during S phase. Because of the pattern of H3 K56Ac during S phase, the Zhang and Verreault labs investigated the possibility that H3 K56Ac may also play a role in nucleosome assembly [9]. They found that H3 K56R mutants are not redundant with mutations in the N-terminal tails of H3 and H4 that are also important for nucleosome assembly.

CAF-1 binds to the histone chaperones Rtt106 and Asf1, both of which are involved in nucleosome assembly [11]. The authors found that all three of these histone chaperones are associated with H3 acetylated at K56. Importantly, they also established that H3 K56Ac promotes the association of H3 with CAF-1 and Rtt106 *in vivo* and *in vitro*. These data suggest a mechanism by which acetylation of K56 may promote assembly, and indeed, H3 K56Ac is important for nucleosome assembly both *in vivo* and *in vitro* ([11], Fig. 1).

Interestingly, they identify a region of Rtt106 that appears to be important for mediating the specific interaction with K56-acetylated H3 [11]. This region is a PH-like domain, such as that found in the Pob3 subunit of FACT, and thus identifies a new potential class of acetyllysine binding motifs.

While the authors do not directly demonstrate that the genome instability of the *H3 K56* mutant strain is due to defective nucleosome assembly, strains lacking other components of this pathway display similar phenotypes, suggesting that this is indeed the case.

In a second report in the same issue of Cell, the Tyler lab also comes to the conclusion that H3 K56Ac plays a role in nucleosome assembly [10]. However, in this case, rather than looking at replication-coupled assembly, Chen et al. exam-

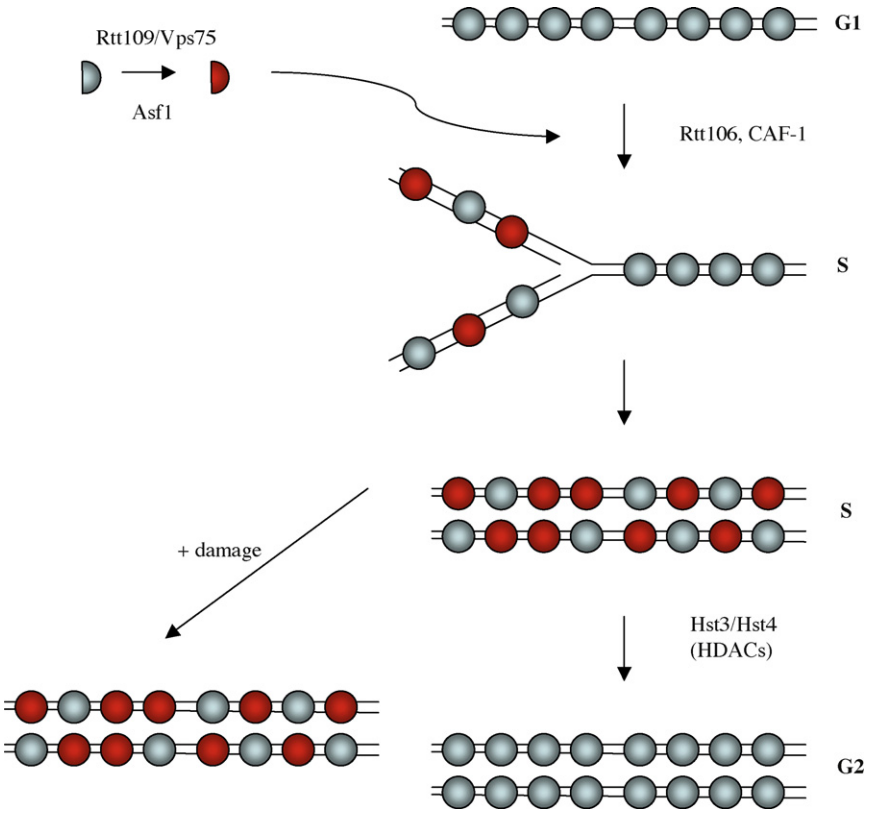

Fig. 1 – Chromatin assembly is dependent on the H3 lysine 56 acetylation pathway. Histone H3 is acetylated by Rtt109/Vps75 at lysine 56 in an Asf1-dependent manner. The acetylated form of the protein is deposited onto newly replicated DNA by the chromatin assembly proteins CAF-1 and Rtt106. The Hst3 and Hst4 deacetylases remove K56Ac during late S/G2 in the absence of DNA damage. When damage is present, their activity is inhibited and the mark persists. Unacetylated H3/H4 dimers are represented by grey half circles, and nucleosomes by grey full circles. H3–H4 dimers and nucleosomes containing acetylated H3 K56 are red.