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Chromatin dynamics

Flipping the switch on a chromatin remodeling machine

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Organization of eukaryotic genomes into compact, nucleoprotein fibers is key for stuffing a lot of DNA into a tiny nucleus, but these structures also create a requirement for machineries that promote DNA accessibility for nuclear processes such as gene transcription, DNA repair, recombination, and replication. Arguably the most notable of such machineries is a large family of ATP-dependent chromatin-remodeling enzymes.[1] These are typically multi-subunit enzymes that perform the "heavy lifting" of chromosome dynamics, as they can use the energy from ATP hydrolysis to unfold chromatin fibers, mobilize nucleosomes within the fiber, evict histone components of the nucleosome, or catalyze incorporation or removal of variant histones that have distinct biochemical properties. These enzymes harbor an ATPase subunit that is related to the SF2 superfamily of DNA helicases, and although these enzymes lack helicase activity, several enzymes have ATP-dependent DNA translocase activity that is likely central for their remodeling activities.

As one might expect, these potent chromatin-remodeling enzymes are tightly regulated within cells, and four basic strategies have emerged[2,3]: (1) direct interaction with sequence-specific DNA binding proteins can target their activity to specific loci; (2) posttranslational modification of remodeling enzymes can modulate enzymatic activity; (3) binding of non-histone proteins to nucleosomal arrays can block remodeling activity and function as molecular "shields"; and (4) histone modifications can regulate remodeling. In most cases, these mechanisms serve to restrain remodeling activity, but our recent work uncovered a novel role for histone acetylation in altering the substrate specificity and overall activity of the SWR-C and INO80 remodeling enzymes.[4]

Yeast SWR-C and INO80 are members of a subfamily of chromatin-remodeling enzymes conserved in all eukaryotes.[5] A crucial role for these multi-subunit enzymes is to control chromosomal distribution of the H2A.Z histone variant that marks nucleosomes at promoters of protein-coding genes, replication origins, centromeres, and chromatin boundary elements. SWR-C is essential for H2A.Z deposition. It evicts H2A/H2B dimers from a nucleosome and replaces them with H2A.Z/H2B dimers in an ATP-dependent reaction. In contrast, INO80 catalyzes the reverse reaction, removing H2A.Z and replacing it with H2A.[6] Recently, we discovered that acetylation of histone H3-K56 disrupts the substrate specificity of SWR-C, allowing it to perform like a combination of SWR-C and INO80, whereby it can catalyze deposition of either H2A.Z or H2A into nucleosomal substrates.[4] These studies suggested a model where H3-K56Ac promotes cycles of continuous dimer exchange that lowers H2A.Z levels at promoters and stimulates nucleosome turnover (**Fig. 1**).

How does acetylation of a single histone lysine regulate SWR-C substrate selectivity? When SWR-C catalyzes replacement of H2A/H2B with H2A.Z/H2B dimers, the Swc2 subunit of SWR-C may bind the H2A.Z nucleosome and prevent activation of the Swr1 ATPase. In the absence of Swc2, the inhibition of Swr1 is relieved, the H2A.Z nucleosome is aberrantly recognized as a substrate, and a second round of dimer exchange ensues.[4] Thus, SWR-C functions much like a machine that can recognize reaction intermediates and steer them to the final product. And in this context, H3-K56Ac functions as a regulatory switch that alters the reaction cycle by directly, or indirectly, impacting Swc2 function.

Swc2 is the primary H2A.Z binding subunit within SWR-C, and it shares homology with mammalian YL-1, a subunit of related Srcap and Tip60 complexes. Interestingly, yeast INO80 also contains a subunit with homology to YL-1, called Ies6, which is essential for INO80 function.[7] It seems likely that Ies6 might also control dimer exchange activities of INO80, much like the role of Swc2 within SWR-C. Since H3-K56Ac also stimulates the dimer exchange activity of INO80, perhaps this histone mark also impinges on Ies6 functions. Whereas Swc2 and YL-1 share an abundance of both basic and acidic residues within their N-terminal regions, Ies6 lacks the acidic region. This suggests a simple model where Swc2 interacts with both DNA and histones, and Ies6 may play a more general role in coupling INO80 activity to nucleosomal DNA.

The acetylation of H3-K56 occurs on free, newly synthesized histones, and thus this mark is abundant within newly replicated chromatin.[8] H3-K56Ac stabilizes stalled replication forks by an unknown mechanism, but persistent H3-K56Ac is also deleterious for genome stability. Consequently, this mark is removed from bulk chromatin by the Hst3 and Hst4 deacetylases at the end of S phase.

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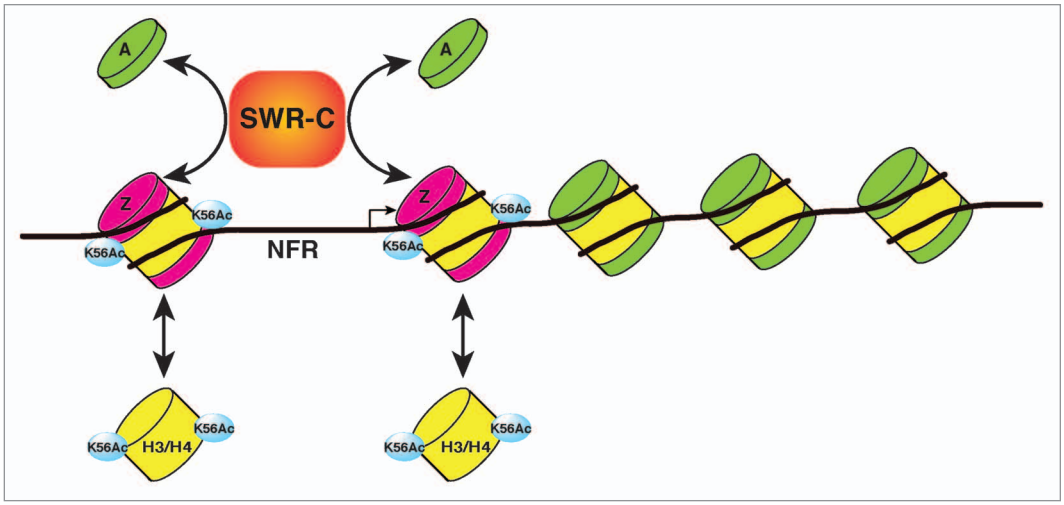

Figure 1. Regulatory interaction between SWR-C and H3K56Ac mediates multiple cycles of histone-exchange. While SWR-C only catalyzes H2A.Z deposition on unacetylated nucleosomes, SWR-C can catalyze both deposition and eviction of H2A.Z on H3-K56Ac nucleosomes, leading to high turnover of H2A.Z.

Whether these enzymes also regulate levels of H3-K56Ac in interphase is not yet known. Interestingly, SWR-C is also required for growth in conditions of replication stress, suggesting that H2A.Z might also play a role during S phase. Furthermore, the combination of H2A.Z deposition behind the fork and high levels of H3-K56ac on the new, daughter nucleosomes might generate a cell cycle window with highly dynamic nucleosomes. This dynamic state might be key for the stability of stalled forks, or it might facilitate other fork-associated events, such as DNA mismatch repair. Given the key role of H2A.Z in nearly every nuclear process, and the abundance of H3-K56Ac, it seems likely that there will be many examples where this regulatory interaction is exploited.

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