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DNA repair: Chromatin remodeling without H2A.Z?

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Chromatin is a highly dynamic structure regulated by different factors, such as ATP-dependent remodeling complexes, incorporation of histone variants, post-translational modifications, and histones chaperones. During the DNA damage response, the chromatin architecture must be transiently and locally modified in order to regulate access to the DNA lesion. Chromatin remodeling at double-strand breaks is necessary, and the recruitment of remodeler complexes such as INO80, SWI/SNF-BRG1-RSC, FUN30, as well as the SWR1/p400 has been observed. Post-translational modifications of histones, such as phosphorylation, ubiquitination, and acetylation at sites of damage are also important to regulate the subsequent repair and cell cycle checkpoint activation/release. Moreover the H2A variant H2A.X is a well-documented player whose phosphorylation is a primary event to initiate the signaling cascade and stabilize the association of multiple factors.

H2A.Z is another H2A variant, incorporated by SWR1 in yeast and SRCAP or p400 in higher eukaryotes. H2A.Z has been proposed to create a region of "poised" chromatin near the transcription start site of genes, facilitating nucleosome disruption during gene activation, in part through its acetylation. It is also important for the establishment of heterochromatin domains near centromeres and at telomeres. H2A.Z is essential in higher eukaryotes, while deletion of the yeast homolog Htz1 is viable. The NuA4 acetyltransferase complex cooperates with SWR1 in targeting chromatin and Htz1 at promoter regions.[1] *Drosophila* homolog H2Av, which functionally represents both H2A.X and H2A.Z, is acetylated and exchanged on chromatin by the TIP60/p400 complex, equivalent to a physical merge of yeast NuA4 and SWR1.[1] Yeast H2A.Z impacts DNA repair by homologous recombination, as sumoylated-Htz1 is transiently incorporated at DNA damage, where it regulates DNA end resection and RAD51 nucleofilament formation.[1] Several groups have attempted to transpose a similar model in mammals, but the conclusions remain unclear.

p400 is recruited to DNA double-strand breaks (DSBs), at least in part within the hNuA4/TIP60 acetyltransferase complex. It has been proposed to function with Tip60 for the acetylation and ubiquitination of chromatin and subsequent recruitment of BRCA1 and 53BP1 to the break.[2] Recent work indicates that p400 is required for DNA repair by Rad51-mediated homologous recombination (HR).[3] In parallel, another study proposed that H2A.Z is transiently exchanged onto nucleosomes at the break by p400.[4] As previously argued for p400, H2A.Z also appears to regulate both acetylation and ubiquitination of chromatin. It was suggested that H2A.Z deposition is important for BRCA1 and Ku70/80 loading and restricts DNA end resection. Thus, H2A.Z could impact the choice between homologous recombination and non-homologous end joining through regulation of CtIP. In contrast to these findings, Canitrot, Trouche, and colleagues now present divergent results.[5] Their data indicate that while H2A.Z is crucial for cell proliferation, viability, and cell cycle regulation, no incorporation is seen at DSBs, as tested by immunofluorescence and chromatin immunoprecipitation. The authors suggest that cell line dependency and p53 status are key issues that may explain the contradictory results, highlighting the bias of cancer vs. immortalized cell lines. They propose that p400 function at the break is independent of H2A.Z incorporation and rather occurs mostly through the TIP60 complex and the acetylation of chromatin. This hypothesis concurs with the actual model, in which acetylation of H4 by TIP60 blocks 53BP1 recruitment to favor HR.[6] Previous reports also implicate the TIP60–p400 complex in acetylation and exchange of phospho-H2A.X at the break.[1]

In the chromatin field, H2A.Z has been a focal point of debate because of reported opposing functions. It must be considered that the role of H2A.Z may be restricted to a certain type of DNA damage, and data about its transient recruitment could be difficult to evaluate. The different studies underline the caveats of studying a factor that affects various cellular processes, most importantly cell proliferation, leading to potential indirect effects, as, in fact, it was proposed for p400 itself.[7] It is also important to consider that the interpretation of ChIP experiments is dependent on the quality of the antibodies and the use of appropriate controls and normalization. Notably ChIP experiments at DSBs should be carefully handled because of (1) the resection process that obviously affects nucleosome occupancy/DNA accessibility for extraction/shearing and (2) the use of reporter systems that depend on cassettes driven by a strong promoter incorporated within the genome. More work is apparently required to elucidate the exact role of H2A.Z/TIP60-p400 during the DNA damage response and the function of H2A.Z eviction or incorporation near DSBs. This is certainly an important question that is raised again by work just published in *Nature* showing that histone chaperon ANP32E associates with TIP60-p400 to help remove H2A.Z from chromatin.[8]

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