Elucidating the role of histone acetylation in regulating chromatin dynamism in *Saccharomyces cerevisiae*

ABSTRACT

In eukaryotes, the compaction of DNA into chromatin creates barriers to accessibility during crucial DNA processes, such as replication, transcription, and repair. However, far from being static, the fluid nature of chromatin exhibits a continuous dynamism between compact and relaxed structures. Such dynamicity is intricately governed by several factors, including histone post-translational modifications that ensure precise regulation of DNA templated processes. Notably, histone lysine acetylation, which neutralizes the positive charge on specific histone residues, emerges as the most widespread and significant amongst the post-translational modifications. This study delves into the influence of histone acetylation on chromatin dynamics during specific DNA-templated processes such as Nucleotide Excision Repair (NER) and transcription. The work specifically explores the impact of acetylation on the 56th lysine residue of histone H3 (H3K56) during NER and transcription. H3K56 acetylation is a unique residue present in the globular core of histone H3 that is recognized for weakening the association of DNA with the histone octamer thus critically influencing DNA unwrapping and accessibility. In eukaryotes efficient NER relies on a substantial stretch of naked DNA for large repair protein complexes to access the DNA damage site. This study demonstrates that acetylation of H3K56 is crucial for DNA accessibility during NER occurring in a chromatin milieu. Utilizing H3K56 mutants, H3K56Q and H3K56R, mimicking constitutively acetylated and unacetylated lysine it was revealed that H3K56 acetylation regulates early NER events. H3K56 acetylation is found to be a pre-requisite for recruitment of crucial repair factor, Rad16, with constitutive acetylation facilitating Rad16 recruitment independently of UV exposure. Additionally, H3K56 acetylation is crucial for UV-induced hyperacetylation of H3 N-terminal tail residues, specifically H3K9 and H3K14. Therefore, the absence of H3K56 acetylation impedes UV-induced recruitment of Rad16 and compromises NER efficiency by affecting H3K9 and H3K14 hyperacetylation. Notably, the UV-induced oscillation of chromatin architecture between compact and relaxed states, characteristic of NER, is distinctly absent in the absence of H3K56 acetylation. In vitro studies using cell extracts from H3K56 mutants further emphasized the involvement of H3K56 acetylation in nucleosome modulation and DNA

Preeti Khan

accessibility during NER. Besides NER, the study also demonstrates that H3K56 acetylation is crucial in regulating RNAPII-dependent transcription within active gene regions. The "histone code" hypothesis proposes that the complex interplay of histone modifications is a key determinant that shapes the chromatin landscape. The findings of this study uncover an intricate interplay between H3K56 acetylation and deacetylation of the H4 N-terminal tail residue H4K16, that collectively facilitate the progression of RNA polymerase II through the gene body of active genes. The results indicate a sequential relationship where H4K16 deacetylation precedes and induces H3K56 acetylation. Significantly, the recruitment of Rtt109, the histone acetyltransferase responsible for H3K56 acetylation, is found to be essentially dependent on H4K16 deacetylation. In strains with Hos2 deletion, where H4K16 deacetylation is impaired, both H3K56 acetylation and RNA polymerase II recruitment are significantly compromised. Remarkably, the dynamic interplay of H4K16 deacetylation and H3K56 acetylation was found to be intricately linked to active transcription. Thus, H4K16 deacetylation serves as a driver for H3K56 acetylation, and the collaborative action of these two modifications is essential for the efficient functioning of RNA polymerase II during active transcription.

In summary, this study highlights the importance of H3K56 acetylation, emphasizing its impact in the establishment of a histone code that intricately governs chromatin accessibility during the process of NER as well as its broader role in moulding the chromatin environment that distinctly influences the outcomes of processes such as transcription.

Preeti Khan