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Chromatin fatigue: An epigenetic legacy of DNA repair

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Abstract

While genomic instability is a hallmark of aging, and unrepaired or mutagenic double-strand breaks (DSBs) are established drivers, recent evidence suggests that even accurately repaired DSBs contribute to aging. Here, we focus on an intriguing study by Bantele *et al.* published in *Science*, which demonstrates that Cas9-induced DSB repair can induce persistent, heritable alterations in higher-order chromatin structure and function, termed "chromatin fatigue". These alterations, characterized by changes in chromatin topology and gene expression, persist long after DNA sequence restoration and are inherited through cell divisions. Crucially, they impair transcriptional responsiveness to physiological stimuli. This finding provides a novel mechanism for DNA damage-driven aging independent of mutations, potentially explaining age-related epigenetic dysfunction. The commentary also highlights key unresolved questions regarding the permanence, locus-specificity, and physiological impact of chromatin fatigue, and explores its interaction with age-related DNA repair decline. This striking molecular phenomenon challenges the notion that faithful repair ensures full functional restoration and opens avenues for future research into interventions against aging and other age-related diseases, such as cancer.

Keywords: Chromatin fatigue, DNA repair, double-strand break, aging, epigenetics

The three-dimensional (3D) architecture of the eukaryotic genome provides a foundational scaffold for the precise regulation of gene expression. Key structural elements, such as topologically associating domains (TADs) and chromatin compartments, maintain genomic functional integrity by coordinating interactions between regulatory elements and their target genes[1,2]. Genomic instability is an established hallmark of aging, and DNA damage accumulation is a major driver of this instability[3]. The intricate relationship between the repair of DNA double-strand breaks (DSBs), the most severe form of DNA damage, and the aging process has long been a research focus[4]. Conventionally, the primary threat posed by DSBs has been considered their potential to cause sequence alterations (such as mutations) or trigger inflammatory responses, thereby driving aging phenotypes[5,6]. However, emerging evidence indicates that even accurately repaired DSBs contribute to aging[7], although the precise underlying mechanisms remain unclear.

A recent *Science* study by Bantele *et al.* reports that DSB repair can induce a heritable form of genome functional impairment termed "chromatin fatigue"[8] (Figure 1). This finding provides a possible mechanism for the long-term consequences of DNA damage independent of mutations and a potential contributor to biological aging and cancer. Focusing on the *c-MYC* locus, the study employed a specifically designed Cas9-induced DSB system targeting 12 sites across its 2.8 Mb TAD region. Results demonstrate that persistent alterations remain long after DNA sequence integrity is restored, including chromatin topological rearrangement, increased local compaction, reduced *c-MYC* expression, and decreased RNA retention within the *c-MYC* TAD[8]. This chromatin dysfunction exhibits significant distance-dependent effects on transcription, where DSB sites closer to the *c-MYC* gene induce more robust transcriptional repression. Notably, this aberrant chromatin state is stably heritable through cell division. The authors demonstrated that daughter cells inherit both the chromatin topological perturbations and the repressed gene expression phenotype from parent cells.

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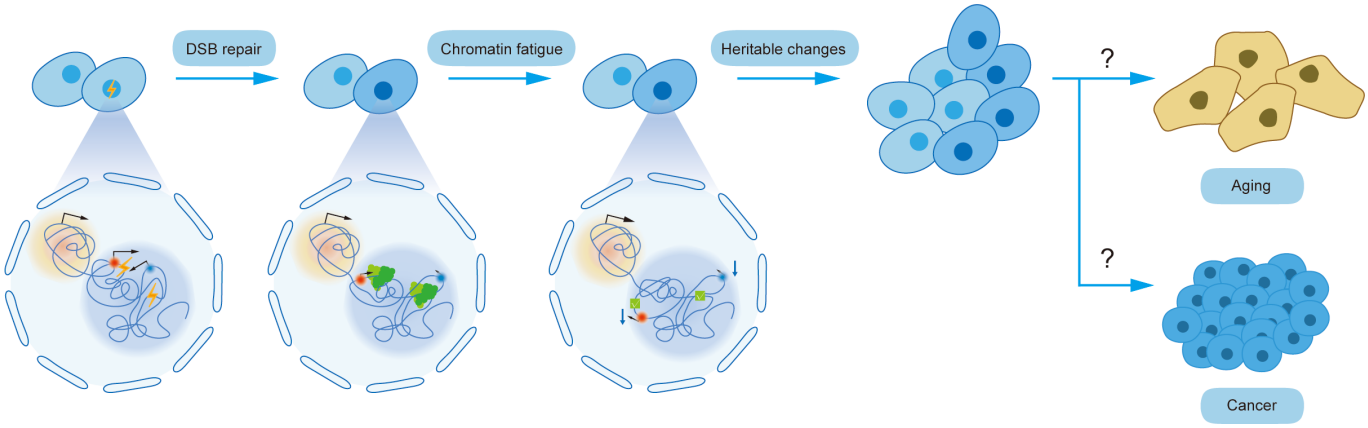


Figure 1. Repair of DNA double-strand breaks causes chromatin fatigue. DSB: double-strand break.

This study raises many interesting questions for future research. First, it is crucial to investigate if the DNA repair initiated by endogenous DSBs results in changes similar to those caused by Cas9-induced repair. DSBs can be repaired via distinct subpathways. The choice of pathway is influenced by multiple factors, including the chromatin context where the damage occurs and the nature of the DNA ends[9]. Consequently, the physiological relevance of Cas9-induced DSBs as a model for the diverse spectrum of endogenous lesions must be further evaluated. Second, histone modifications play important roles in regulating gene expression. A key question is whether successful DSB repair, beyond altering topology, also influences the histone modifications surrounding the damage sites. Moreover, in their study, Bantele *et al.* induced a single DSB and observed significant consequent changes. Given that an estimated 10-50 DSBs occur per cell per day in mammals[10,11], a key question arises: how does the simultaneous occurrence of DSBs at multiple genomic loci impact chromatin topology and histone modifications? This warrants further investigation. Additionally, although the authors confirmed that these persistent chromatin alterations can be passed through cell division, a key unresolved question is their duration. Are these changes truly permanent, or can they be gradually restored over extended cell divisions? Future work involving extended lineage tracing is needed to answer this question.

While DNA sequence integrity can be restored upon faithful DNA repair, whether higher-order chromatin architecture and its functional state are fully restored post-repair remains unclear. This study provides evidence that damage-induced changes in higher-order chromatin architecture may not be repaired. Determining the long-term consequences of these changes is an intriguing future direction. Epigenetic dysregulation has been proposed as another primary hallmark of aging. Based on unique age-related alterations in DNA methylation patterns, multiple DNA methylation-based epigenetic clocks have been established in recent years to predict biological age[12-15]. While these clocks are widely used in aging research, the upstream drivers of this epigenetic drift remain obscure. Given the prevalence of endogenous DNA damage, Bantele *et al.* provide a potential mechanistic explanation for age-associated epigenetic changes. In addition, responsiveness to regulatory cues is essential for tissue homeostasis. The authors showed that persistent chromatin alterations blunt this responsiveness, as cells exhibit reduced *c-MYC* responsiveness to upstream signaling even when DSBs occur outside its coding region. This impairment may hinder cellular adaptability to changing environments or responsiveness to stimuli, potentially contributing to age-related functional decline. Previous work, including our own, has demonstrated an age-related decline in DNA repair capacity[16]; for example, we have shown that XRCC4 transcription declines with age[17,18]. An interesting question is how impaired DNA repair processes influence the chromatin fatigue phenotype. Could decreased repair capacity increase the likelihood and severity of these alterations? Conversely, efficient DNA repair is associated with longevity, and activation of DNA repair pathways contributes to delayed aging and reduced age-related degenerative decline[19-23]. Could we potentially ameliorate these chromatin alterations by actively enhancing DNA repair? These questions warrant further exploration. But first, it must be established whether the chromatin fatigue phenotype is present in naturally aged cells or organisms.

Is chromatin fatigue involved in oncogenesis and tumor development? Advances in research techniques have revealed alterations in the 3D genome in cancer[24]. Given the rapid proliferation and high metabolic activity of cancer cells, a large number of DSBs are likely to occur due to replication stress and reactive oxygen species. However, it remains unclear whether a causal link exists between such DNA damage and the observed spatial genome reorganization in cancer. Furthermore, mutations in DNA repair factors are known to facilitate tumorigenesis[25,26]. Similar to the discussion on aging, a key question is how such DNA repair deficiencies impact chromatin fatigue and, consequently, modulate cancer progression. Notably, studies have also indicated that epigenetic alterations compromise DNA damage recognition and repair in cancer[27]. This raises an additional question: could chromatin fatigue, in turn, impair DNA repair processes, thereby establishing a vicious cycle that exacerbates both repair deficiency and chromatin disorganization? Finally, a key future goal should be to explore whether targeting chromatin fatigue can lead to new interventions for cancer.

In summary, this study establishes persistent chromatin alterations as a key mechanistic link between DNA damage repair and

epigenetic dysfunction, challenging the traditional paradigm that efficient DNA repair ensures full functional restoration. Future research addressing unresolved questions regarding the reversibility, locus specificity, and physiological relevance of these alterations will further solidify the role of chromatin fatigue in aging and cancer and could potentially inform new therapeutic strategies for healthy longevity.

Declarations

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The authors declare that the Deepseek-V3 was used solely for language polishing during the manuscript preparation process. All research content, including study design, interpretations, and figures was not generated using AI tools.

Authors contribution

Chen Y: Conceptualization, writing-review & editing, funding acquisition.
Chen L: Writing-original draft, writing-review & editing.
Mao Z: Funding acquisition.

Conflicts of interest

Zhiyong Mao is an Associate Editor, and Yu Chen is a Youth Editorial Board Member of *Ageing and Cancer Research & Treatment*. The other author declares no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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