Cancer Biol Med 2025. doi: 10.20892/j.issn.2095-3941.2025.0369

PERSPECTIVE

Chromatin relaxation dynamics and histone PTMs in the early DNA damage response

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During cellular proliferation DNA undergoes frequent replication cycles in which errors inevitably accumulate. DNA simultaneously faces continuous damage from endogenous sources [e.g., reactive oxygen species (ROS)] and environmental stressors, such as ultraviolet (UV) and ionizing radiation (IR). Such lesions compromise genomic stability and may escalate into DNA double-strand breaks (DSBs). Failure to repair DSBs can ultimately trigger cell death[1].

The DNA damage response (DDR) involves a coordinated, multi-step process with precise lesion detection followed by controlled chromatin remodeling to facilitate repair. Initially, the cell identifies and localizes damage sites. Then, the cell remodels condensed chromatin and constructs a platform to recruit various DNA damage repair factors to access DNA lesions. These factors excise or replace the damaged segment to repair DNA. Following repair completion, dedicated machinery restores chromatin to a closed conformation, thereby maintaining genomic integrity, a process collectively termed the Access-Repair-Restore (ARR) model[2].

Chromatin, which is comprised of DNA coiled around histone octamers (H2A/H2B/H3/H4) and stabilized by a linker (histone H1), compacts the genome into a nucleosome. This condensed architecture intrinsically obstructs DNA repair machinery, impeding repair factor recruitment. The earliest chromatin relaxation, which is essential for initiating repair, remains mechanistically opaque.

Elucidating the spatiotemporal dynamics of chromatin relaxation during early DNA damage response is imperative. Therefore, we summarized pioneering advances in understanding how histone modifications and remodelers orchestrate chromatin relaxation and accessibility.

PARylation orchestrates early chromatin remodeling at DNA lesions

Poly(ADP-ribosyl)ation (PARylation) is a rapid post-translational modification catalyzed by poly(ADP-ribose) polymerases (PARP) enzymes that covalently attaches poly(ADP-ribose) chains to target proteins, particularly core histone, within seconds of DNA damage detection. This modification introduces massive negative charges onto histones, fundamentally altering the electrostatic properties. The resultant charge repulsion disrupts histone-DNA interactions and induces local chromatin decondensation, priming the damaged site for repair machinery access[3].

During the earliest phase of DDR PARylation dominates histone dynamics by directly mediating eviction of histones within minutes. Genome-wide analyses reveal that this eviction extends bidirectionally up to 4 kb from DSBs, creating a permissive chromatin domain. Notably, PARylation precedes γH2AX phosphorylation and H2A ubiquitination. PARP inhibition, unlike ATM/DNA-PK inhibition, delays histone eviction by > 30 min, establishing PARylation as the early trigger in this cascade. Mechanistically, PAR chains recruit histone chaperones *via* specific interaction domains. For example, the

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Received July 9, 2025; accepted September 4, 2025;
published online October 9, 2025.
Available at www.cancerbiomed.org

facilitates chromatin transcription (FACT) complex, through the structure-specific recognition protein 1 (SSRP1) subunit, binds PARylated histones *via* a C-terminal PAR-binding motif. This recruitment enables FACT-dependent nucleosome disassembly, as evidenced by abolished histone eviction upon SSRP1 knockout. This pathway explains why PARP inhibitors impair the initial repair steps. Specifically, delayed histone clearance physically blocks repair factor access to DSBs[4,5].

Histone PARylation critically regulates chromatin remodeling factors during the DDR[6]. The addition of negatively charged PAR chains to histone tails serves as a molecular scaffold for recruiting ATP-dependent remodelers, including amplified in liver cancer 1 (ALC1) and chromodomain helicase DNA-binding protein 2 (CHD2)[7]. PAR binding activates ALC1, enabling nucleosome sliding and increased DNA accessibility. Likewise, PARylated histones recruit CHD2, which facilitates the incorporation of the histone variant, H3.3, to promote chromatin relaxation[7]. These PAR-dependent remodeling events are essential for establishing an open chromatin state that supports the assembly of DNA repair complexes.

In addition to recruiting chromatin remodelers, histone PARylation mediates the localization of repressive complexes, such as nucleosome remodeling and histone deacetylation (through CHD4) and protein regulator of cytokinesis 1, to regions flanking DNA damage sites[8]. This spatial organization enables localized chromatin decompaction at the lesion, while simultaneously inhibiting transcription in nearby regions, thus preventing interference between repair and transcriptional machinery. The dynamic turnover of PAR, which is controlled by PARP1-dependent synthesis and degradation by poly(ADP-ribose) glycohydrolase and ADP-ribosylhydrolase 3, ensures precise temporal regulation of these chromatin remodeling processes[9].

The linker histone, H1.2, functions as a steric barrier restraining ataxia telangiectasia mutated (ATM) kinase activation by sequestering ATM kinase from the MRE11-RAD50-NBS1 (MRN) complex *via* direct binding[10]. Upon DNA damage PARP1 rapidly catalyzes PARylation at Ser188 within the H1.2 C-terminal domain. This PARylation triggers immediate (< 10 s) H1.2 dissociation from chromatin through electrostatic repulsion and structural remodeling. Chromatin accessibility permits MRN-dependent ATM recruitment and activation. Critically, PARylated H1.2 undergoes subsequent proteasomal degradation, ensuring persistent ATM signaling. Inhibition of PARylation *via* PARP inhibitors or H1.2-S188A mutation stalls H1.2 displacement, compromising ATM autophosphorylation (pS1981), downstream checkpoint activation, and DSB repair efficiency. This pathway elucidates a PAR-dependent chromatin relaxation mechanism wherein H1.2 eviction serves as a molecular gatekeeper for ATM-driven DDRs (**Figure 1A**). The exquisite specificity for H1.2 highlights the unique role in bridging initial chromatin alterations to repair fidelity and cell survival[10].

PARP1 inhibitors have shown significant efficacy in cancer treatment, especially for breast cancer (BRCA)-deficient cancers. However, the emergence of drug resistance remains a major clinical challenge[11]. Growing evidence highlights the importance of histone PARylation, an early chromatin modification triggered by DNA damage[12]. Understanding how PARP1-mediated PARylation regulates DNA repair, chromatin structure, and downstream signaling will provide deeper insights into resistance mechanisms and facilitate the development of new therapeutic strategies.

Histone H1 deamidation: a metabolic epigenetic switch governing chromatin accessibility in DNA repair

Unlike spontaneous deamidation, which is historically viewed as a non-enzymatic "aging" process, glutamine amidotransferases (GAT)-mediated deamidation exhibits precise substrate specificity[13,14]. Deamidation reprograms protein polarity by enzymatically converting neutral glutamine/asparagine side chains to anionic glutamate/aspartate residues. This transformation introduces localized negative charges that disrupt electrostatic equilibria and hydrogen-bond networks. Deamidation acts as a molecular switch by altering protein surface electrostatics, repurposing metabolic enzymes into signaling regulators. For example, deamidation disrupts dsRNA recognition in retinoic acid-inducible gene I and DNA binding in cyclic GMP-AMP synthase by shifting domain polarity[15]. Deamidation creates acidic patches that redirect transcriptional activity from inflammatory to metabolic genes in Re1A[16].

The GATs family encompasses multifunctional metabolic enzymes, including carbamoyl-phosphate synthetase 2, aspartate transcarbamoylase, dihydroorotase (CAD), cytidine 5′-triphosphate synthases (CTPSs), and phosphoribosyl pyrophosphate amidotransferase/phosphoribosyl formylglycinamidine synthase (PPAT/PFAS)[13]. CTPS1 emerges as a critical orchestrator of genomic stability because dysregulation

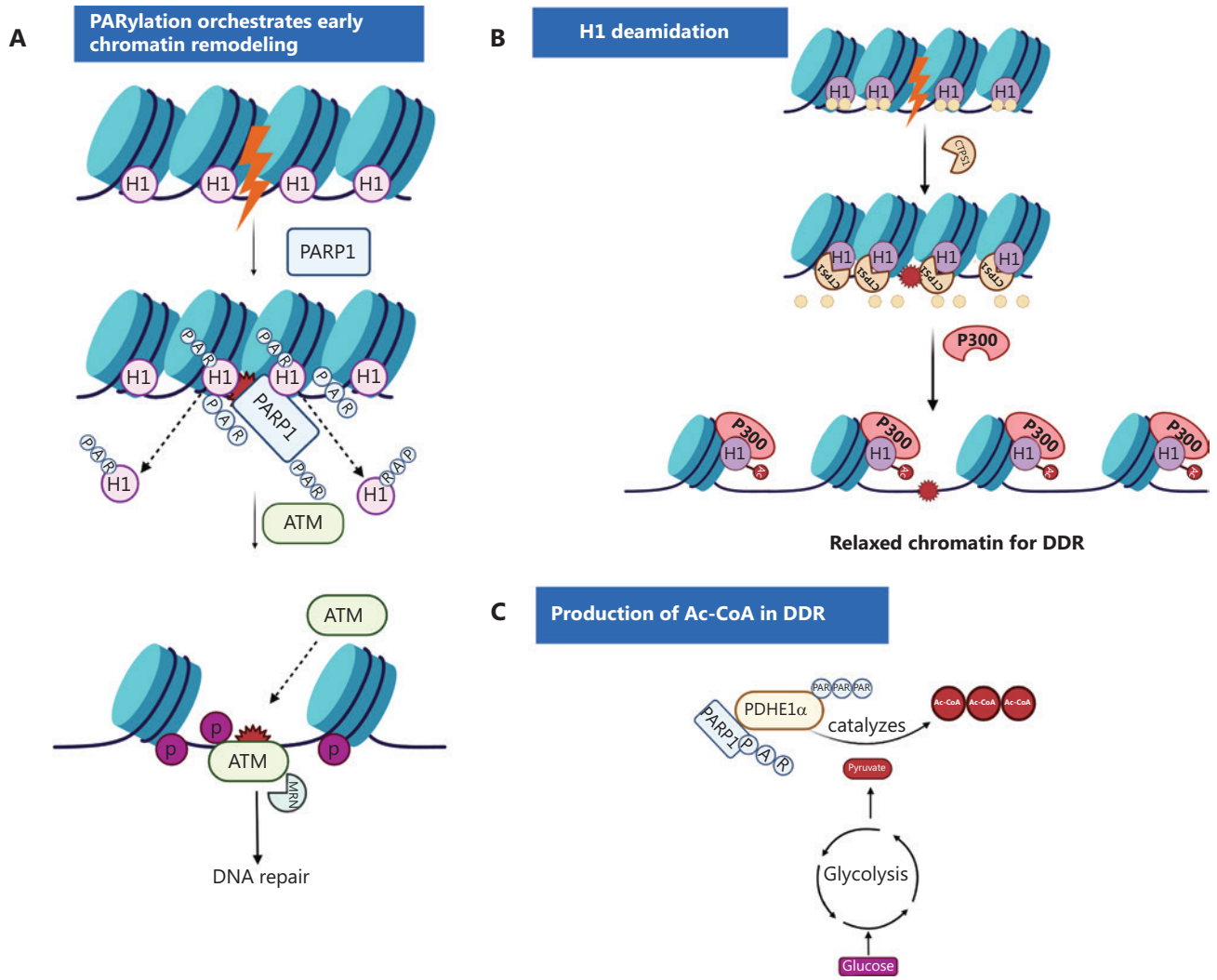

Figure 1 Mechanisms of early chromatin relaxation in the DNA damage response. (A) Upon DNA damage, PARP1 rapidly accumulates at lesions and catalyzes PARylation of the linker histone, H1.2, at Ser188. This modification introduces extensive negative charge, triggering electrostatic repulsion-mediated dissociation of H1.2 from chromatin. H1.2 eviction removes its steric blockade of ATM kinase, enabling recruitment and activation of the MRE11-RAD50-NBS1 (MRN) complex. Consequently, ATM-dependent signaling initiates DSB repair. (B) The metabolic enzyme, CTPS1, is recruited to DSBs where CTPS1 catalyzes enzymatic deamidation of asparagines 76/77 (N76/N77) in the globular domain of histone H1.4, converting N76/N77 to aspartate (N76D/N77D). This charge conversion reduces H1.4-DNA affinity and creates a binding site for the acetyltransferase, p300. p300 subsequently acetylates adjacent lysine 75 (K75ac), synergistically weakening H1.4-DNA interactions to drive large-scale chromatin relaxation. C. PDHE1α is recruited to DSBs *via* PAR-binding and undergoes PARP1-mediated PARylation. Chromatin-tethered PDHE1α catalyzes nuclear pyruvate to generate localized acetyl-CoA pools directly at damage sites. This fuels histone acetyltransferases, enabling rapid acetylation of histones. ATM, ataxia telangiectasia mutated; CTPS1, CTP synthase 1; DDR, DNA damage response; DSBs, double-strand breaks; MRN, MRE11-RAD50-NBS1; PAR, poly(ADP-ribose); PARP1, poly(ADP-ribose) polymerase 1; PDHE1α, pyruvate dehydrogenase 1α.

of CTPS1 directly promotes replication stress and DNA damage in hyperproliferative cancers. CTPS1 maintains dNTP pool homeostasis essential for DNA replication fidelity as the rate-limiting enzyme for CTP synthesis[17]. CTPS1 inhibition depletes dCTP in MYC-driven cancers, which causes S-phase progression with incomplete DNA replication. This inhibition leads to replication fork failure, DSBs, and hyperactivation of the ataxia telangiectasia and Rad3-related protein checkpoint kinase 1 (ATR-CHK1) pathway[18]. CTPS1 inhibition (e.g., *via* STP-B) synergizes profoundly with ataxia telangiectasia and

rad3-related protein, checkpoint kinase 1, or wee1 G2 checkpoint kinase inhibitors because concurrent disruption of replication stress sensors abrogates fork rescue mechanisms[19].

A new study unveiled a fundamental mechanism by which chromatin relaxation, a prerequisite for efficient DNA DSB repair, is initiated through an unexpected post-translational modification involving enzymatic deamidation of the linker histone, H1[20]. While histone acetylation is an established facilitator of chromatin relaxation, activation requires prior remodeling of compacted chromatin. Tian et al. demonstrated that the metabolic enzyme, CTPS1, is rapidly recruited to DSBs, where CTPS1 catalyzes deamidation of asparagines 76 and 77 (N76/N77) in the globular domain of the histone, H1.4. This reaction converts neutral asparagines to negatively charged aspartates, triggering a cascade that directly reduces the H1 DNA-binding affinity[13]. The discovery showed deamidation as the early trigger for chromatin relaxation in the DDR, assigning an unprecedented epigenetic role to a metabolic enzyme.

Mechanistically, H1 deamidation acts as a molecular gateway for subsequent chromatin remodeling. The CTPS1-mediated generation of H1 (N76D/N77D) creates a high-affinity binding site for the histone acetyltransferase, p300[21]. Structural analyses revealed that deamidation induces conformational changes in H1, permitting p300 to acetylate the adjacent lysine 75 (K75). This sequential modification (N76D/N77D followed by K75ac) cooperatively reduced positive charge density at the H1 DNA-binding interface. Biochemical and biophysical assays confirmed that the modified H1 exhibits weakened nucleosome association, leading to large-scale chromatin relaxation. Cells expressing deamidation-resistant H1 mutants (N76A/N77A or N76R/N77R) or CTPS1 catalytic mutants fail to recruit p300, acetylate K75, or relax chromatin after damage, underscoring the strict sequential dependency of this pathway (**Figure 1B**).

This work broadens paradigms in DDR and epigenetic regulation. First, enzymatic deamidation was uncovered as a functionally critical histone modification, expanding the functions of chromatin-regulating post-translational modifications (PTMs)[13]. Second, CTPS1 was repurposed as a sequence-specific histone deamidase, establishing direct crosstalk between cellular metabolism and chromatin dynamics. Third, hierarchical PTM cascades (deamidation preceding acetylation) were shown to govern chromatin accessibility with precision. Targeting CTPS1 deamidase activity offers a promising strategy to overcome radioresistance by opening chromatin architecture at DSBs. More broadly, this pathway illuminates how metabolic enzymes function as epigenetic regulators.

Production of acetyl-CoA for local chromatin acetylation and DDR

The rapid relaxation of chromatin structure at DNA DSBs is a fundamental prerequisite for efficient repair, requiring prompt and localized histone acetylation to neutralize positive charges on lysine residues and facilitate access for repair machinery[22]. A critical, long-unanswered question centers on how cells meet the enormous, spatially constrained demand for acetyl-CoA, which is the essential acetyl-group donor within the immediate vicinity of the DDR[23]. Traditional models have implicated nuclear pools generated by enzymes, like ATP-citrate lyase (ACLY) and acetyl-CoA synthetase (ACSS2), yet the recruitment and activation kinetics appeared insufficient to explain the swiftness and magnitude of acetylation observed at nascent damage sites[24,25]. This spatial and temporal disconnect highlighted a significant gap in understanding the metabolic fueling of the DDR.

Recent work unveiled a pivotal mechanism in which pyruvate dehydrogenase E1α (PDHE1α), a key mitochondrial enzyme, is rapidly recruited to DSB sites in a PARylation-dependent manner[26]. Upon DNA damage PDHE1α binds PAR chains *via* specific motifs and is subsequently PARylated by PARP1. This dual PAR-binding/PARylation event drives the swift accumulation of PDHE1α onto the damaged chromatin. Once localized, PDHE1α catalyzes the decarboxylation of nuclear pyruvate derived from the abundant glucose pool to generate acetyl-CoA directly at the DSB. This reaction creates a highly localized acetyl-CoA pool that fuels histone acetyltransferases (HATs), enabling rapid acetylation of histones (e.g., H3K9ac and H4K16ac) and chromatin-associated proteins within the damaged domain (**Figure 1C**). This process is distinct from and more rapid than contributions from ACLY or ACSS2, positioning PDHE1α as the primary enzyme responsible for the acute, burst-like acetyl-CoA production needed for initial chromatin relaxation[27].

This spatiotemporally regulated production of acetyl-CoA by chromatin-associated PDHE1α is not merely metabolic support. Indeed, it is a decisive regulatory step in genome maintenance[28]. This process licenses the formation of accessible chromatin architecture around DSBs, enabling the efficient loading of repair factors, like BRCA1 and tumor protein P53 binding protein 1[29]. As a result, disruption of PDHE1α recruitment or enzymatic activity severely impairs DSB repair, compromises genome stability, and sensitizes cancer cells to DNA-damaging agents. This mechanism resolves the problem of rapid acetyl-CoA sourcing at DSBs, revealing how

metabolic enzymes are co-opted into the DDR through precise post-translational modifications to locally fuel essential epigenetic remodeling.

Histone acetylation is also a key epigenetic modification that regulates the targeting and activity of ATP-dependent chromatin remodeling complexes, including the inositol auxotroph 80 (INO80), switch defective/sucrose non-fermentable (SWI/SNF), and CHD families[30]. The INO80 complex is recruited to DNA DSBs in an H4 acetylation-dependent manner. There, the INO80 complex catalyzes the exchange of canonical H2A for the H2A.Z variant, facilitating a chromatin state that supports repair[31]. SWI/SNF complexes bind acetylated histones through bromodomains, which directs acetylated histones to specific genomic sites and stimulates nucleosome eviction[32]. CHD remodelers, such as CHD1 and Mi-2, also respond to acetylated nucleosomes *via* chromodomains and associated subunits, enabling modulation of nucleosome spacing and mobility[33]. Beyond recruitment, acetylation can allosterically influence remodeler ATPase activity[30]. Thus, histone acetylation critically orchestrates the localization and functional output of chromatin remodeling machines.

Local acetyl-CoA production by PDHE1α at DNA damage sites fuels rapid histone acetylation, a critical step in chromatin relaxation and repair factor recruitment[34]. Conversely, acetyl-CoA supplementation may hyperactivate histone acetyltransferases in repair-deficient contexts, potentially inducing lethal chromatin hyperaccessibility. These findings highlight acetyl-CoA production as a metabolic vulnerability that can be exploited to disrupt DNA damage repair in cancer therapy[35]. Therapeutic co-targeting of PDHE1α and key acetyl-CoA synthases, such as ACLY and ACSS2, represents a promising strategy to counter metabolic adaptability in treatment-resistant tumors, potentially enhancing therapeutic efficacy and overcoming resistance mechanisms in clinical therapy.

Discussion and future perspectives

The past decade has yielded transformative insights into DDR, revealing dynamic recruitment cascades of repair factors and clinically exploitable synthetic lethal treatment[36]. Despite these advances, the earliest events of DDR initiation, particularly chromatin relaxation and epigenetic reprogramming at the damaged site, remain mechanistically relatively opaque (**Table 1**). These insights into early chromatin remodeling mechanisms provide a foundation for developing next-generation therapies that target the vulnerabilities of repair-proficient tumors with the potential to overcome resistance and improve

Table 1 Key early events in chromatin relaxation during DNA damage response

Molecular event	Key factors/mechanism	Functional consequence for chromatin structure	References
1. Poly(ADP-ribosyl)ation (PARylation)	PARP1 rapidly synthesizes PAR chains on: • Core histones (H2A/H2B/H3/H4) • Linker histone H1.2 (at Ser188)	• Introduces massive negative charges → disrupts histone-DNA electrostatic interactions • Triggers rapid eviction of core histones and H1.2 dissociation • Creates platform for FACT-dependent nucleosome disassembly	3-5,10
2. Histone H1 deamidation	CTPS1 is recruited to DSBs; catalyzes enzymatic deamidation of H1.4 at N76/N77 → N76D/N77D	• Converts neutral Asn to acidic Asp → reduces H1-DNA affinity • Creates binding site for p300 → promotes H1K75 acetylation → chromatin relaxation	20
3. Local acetyl-CoA production	PDHE1α recruited to DSBs *via* PAR-binding; catalyzes nuclear pyruvate → acetyl-CoA at damage sites	• Provide acetyl-CoA for HATs (e.g., p300) → rapid acetylation of histones • Enables chromatin relaxation for repair factor recruitment (BRCA1, 53BP1)	26,36
4. Histone H1 acetylation	PCAF acetylates H1K85; p300 acetylates H1K75	• H1K85ac ↑ → strengthens H1-core histone interaction → promotes chromatin condensation → recruits HP1 →stabilizes heterochromatin • DNA damage reduces H1K85ac → chromatin relaxation for repair	20,37

53BP1, tumor protein P53 binding protein 1; BRCA1, breast cancer 1; CTPS1, CTP synthase 1; DSBs, double-strand breaks; FACT, facilitates chromatin transcription; HATs, histone acetyltransferases; HP1, heterochromatin protein 1; PAR, Poly (ADP-ribose); PARP1, poly(ADP-ribose) polymerase 1; PCAF, P300/CBP-associated factor; PDHE1α, pyruvate dehydrogenase 1α.

patient outcomes. Future research should prioritize real-time dissection of chromatin relaxation kinetics, focusing on the following:

1. How do histone PTMs, including acetylation, PARylation, and deamidation, cooperate or compete to license rapid structural relaxation? The precise spatiotemporal hierarchy and crosstalk among these modifications remain opaque. Investigations have demonstrated that no regulatory interplay exists between PARP1-mediated PARylation and H1 deamidation (N76D/N77D) or H1K75 acetylation following DNA damage, underscoring H1 deamidation and PARP1 function as two parallel pathways driving chromatin remodeling. Future research must clarify the dynamic regulation of histone PTMs in DDR. Currently, there is limited direct evidence describing the interplay and timing between different PTMs in regulating cellular functions. Using time-resolved proteomics, live-cell imaging, and chromatin accessibility assays will be crucial to track the order, relationships, and dependencies of multiple PTMs over time. These methods will help decode the functional networks and combine mechanisms governed by PTM-based histone codes.
2. In addition to histone tail modifications, how do PTMs within structured globular domains regulate higher-order chromatin architecture and function? The globular domain of linker histone H1 has a pivotal role in regulating higher-order chromatin architecture, a critical determinant of DNA accessibility during the DDR. Our previous study also revealed that acetylation of a highly conserved lysine residue (K85) within the H1 globular domain, dynamically regulated by the acetyltransferase p300/CBP-associated factor and the deacetylase histone deacetylase 1, regulates chromatin structure and preserves chromosome integrity upon DNA damage[37]. Future investigations will need to elucidate how modifications within specific structural domains of chromatin regulators orchestrate precise chromatin conformational changes across diverse DNA damage response pathways.
3. While histone deamination has emerged as a key early event in the DDR, the mechanistic interplay with chromatin remodeling factors remains poorly characterized. Future studies focusing on this crosstalk will be essential to precisely delineate the spatiotemporal regulation of chromatin dynamics during the initial phases of DNA damage.
4. How do cellular metabolic pools dynamically influence chromatin remodeling? On the basis of connecting carbohydrate metabolism and nucleotide synthesis to early DNA damage sensing, the emerging paradigm of metabolite-driven chromatin states demands mechanistic dissection. For example, lactate is reported not merely as a metabolic byproduct but as a regulator of DNA damage repair[38,39]. A recent study revealed that lactate serves as a direct substrate for histone lactylation, an emerging form of epigenetic modification[40]. Specifically, increased intracellular lactate levels promote histone H4K12 lactylation, which alters chromatin accessibility and facilitates transcriptional activation of key metabolic genes. This mechanism establishes a direct link between cellular metabolic activity and epigenetic regulation, demonstrating how nutrient availability can shape the epigenome through lactate-dependent signaling. Future studies should resolve how metabolic byproducts directly or indirectly modulate epigenetic machinery at lesion sites, thereby integrating metabolic dysregulation with repair pathway fidelity for therapeutic targeting.

Grant support

This work was supported by grants from the Shenzhen Medical Research Fund (Grant no. A2302040).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the paper: Liqun Zhou and Wei-Guo Zhu
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Cite this article as: Qian J, Xie Z, Zhou L, Zhu W-G. Chromatin relaxation dynamics and histone PTMs in the early DNA damage response. Cancer Biol Med. 2025; 22: 1267-1274. doi: 10.20892/j.issn.2095-3941.2025.0369