



# Nuclear mechanics underlying DNA damage repair

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## Abstract

DNA integrity and stability are intricately linked to DNA damage repair (DDR) pathways, which have long been well characterized through a biochemical perspective. However, the physical properties of the nucleus in which DNA damage occurs have been long overlooked, leaving the relationship between nuclear mechanics and DDR poorly defined. In this review, we describe the core mechanical components, including the lamina, chromatin, and linker of nucleoskeleton and cytoskeleton (LINC) complex, which collectively determine nuclear stiffness, tension, and structural integrity. We further define the regulatory role of nuclear mechanics in DDR, with particular emphasis on DNA double-strand break (DSB) repair. Aberrant nuclear stiffening, tension, and envelope rupture may cause persistent DNA repair failure and genomic instability. Nuclear mechanics are aberrantly altered in cancers, therefore manipulating nuclear mechanics may counteract therapeutic drug resistance via regulating DDR efficiency in cancer cells. Throughout, we conclude that nuclear mechanics acts as a physical rheostat for DDR. Manipulating nuclear stiffness, tension, or envelope integrity susceptibility offers a new therapeutic axis for sensitizing tumors to DNA-damaging agents.

**Keywords:** Nuclear mechanics, DNA damage repair, double-strand break, tumor therapy

## 1. Introduction

Genome stability is perpetually threatened by various DNA lesions. To counter these threats, cells have evolved sophisticated DNA damage repair (DDR) pathways. Depending on the type of DNA damage, distinct repair mechanisms are engaged. A single unrepaired DNA double-strand break (DSB) can trigger cell death, while a mis-repaired DSB can initiate chromosomal translocations, genomic instability, and cancer<sup>[1]</sup>. Non-homologous end joining (NHEJ) and homologous recombination (HR) are two principal pathways to repair DSBs. NHEJ, functioning throughout the cell cycle, is error-prone but reconnects DSB ends directly via TP53-binding protein 1 (53BP1)-favoured repair factors. NHEJ initiation involves KU70/80 heterodimer binding at DSB ends, which subsequently recruits DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to promote the synapsis of loose DNA ends. Final ligation is performed by DNA ligase 4 (LIG4) with X-ray repair cross-complementing protein 4 (XRCC4)<sup>[2]</sup>. In contrast, HR operates only in S/G2 phases and is of high-fidelity via using a sister chromatid as a template. For HR, breast cancer type 1 susceptibility protein (BRCA1) antagonizes 53BP1 and promotes DSB end resection. This process is initiated by the MRE11-RAD50-NBS1 (MRN) complex together with C-terminal binding protein (CtBP)-interacting protein (CtIP), and is subsequently extended by exonuclease 1 (EXO1) and DNA replication helicase 2 (DNA2), in conjunction with helicases such as bloom syndrome RecQ like helicase (BLM) and werner syndrome adenosine triphosphate (ATP)-dependent helicase (WRN), to generate the single-strand DNA ends required for RAD51 loading and homologous pairing<sup>[3]</sup>.

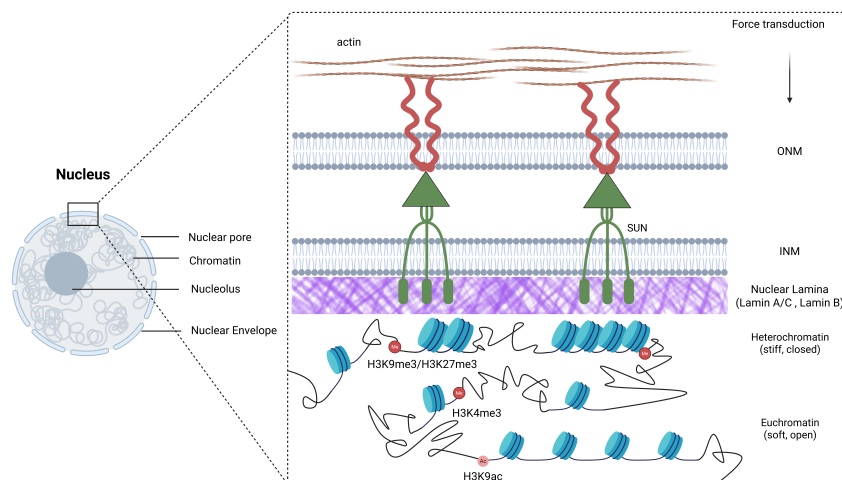
For decades, DDR has been understood through biochemical approaches, which have identified proteins, signaling cascades, and enzymatic reactions that govern DNA repair<sup>[4]</sup>. An emerging perspective recognizes that the nucleus is not only the repository of genomic DNA and the regulatory center of gene expression, but also a physical object with measurable mechanical properties, including stiffness, resistance to deformation, tension, pulling forces from the cytoskeleton, and structural integrity<sup>[5]</sup>. By integrating mechanical forces such as extracellular matrix stiffening, stretching, interstitial fluid pressure, and fluid shear stress on the cell, the nuclear mechanics has emerged as an active participant in core cellular biological processes, including DDR pathways<sup>[6-8]</sup>. In this



review, we describe the components governing nuclear mechanics and discuss the mechanisms underlying how nuclear mechanical properties influence DDR, specifically DSB repair. We also highlight that the regulation of nuclear mechanics in DDR is essential for understanding genomic instability in cancer, offering new therapeutic avenues for cancer treatment.

## 2. Core Components Governing Nuclear Mechanics

The nucleus, the most rigid organelle within the cell, is composed of the nuclear interior, nuclear bodies, and the surrounding nuclear envelope (NE). The nuclear envelope consists of the outer and inner nuclear membranes (ONM and INM, respectively), which partition nuclear contents from the cytoplasm and regulate access of cytoplasmic proteins to the genome<sup>[9]</sup>. Mechanically, it is regulated by three primary components: the nuclear lamina, chromatin, and the linker of nucleoskeleton and cytoskeleton (LINC) complex (Figure 1). Each component imparts mechanical traits to the nucleus and is dynamically remodeled by cellular forces or pathological mutations<sup>[10,11]</sup>.



**Figure 1.** Schematic illustration of core components governing nuclear mechanics. The nucleus is surrounded by the NE, which comprises the ONM and INM. The LINC complex, composed of SUN proteins (located in the INM) and nesprins (located in the ONM), connects the nucleoskeleton to the cytoskeleton through actin filaments. The nuclear lamina, situated beneath the INM, provides structural support and contributes to nuclear stiffness. Within the nucleus, heterochromatin, characterized as stiff and closed, is marked by histone modifications H3K9me3 and H3K27me3, whereas euchromatin, characterized as soft and open, is marked by H3K9ac and H3K4me3. The balance between these chromatin states, in conjunction with the nuclear lamina and LINC complex, collectively determines nuclear mechanics. ONM and INM: outer and inner nuclear membranes; NE: nuclear envelope; SUN: sad1-UNC-84 homology; LINC: linker of nucleoskeleton and cytoskeleton; Lamin A/C: A-type lamins; Lamin B: B-type lamins.

The nuclear lamina is a fibrous proteinaceous meshwork underneath the INM. It interacts with chromatin and plays a key role in structural support, maintaining both nuclear stiffness and shape stability, as well as cellular integrity. The lamina is composed of A-type (lamin A/C) and B-type (lamin B1/B2) intermediate filaments and lamin-associated proteins<sup>[12]</sup>. Among these, lamin A/C functions as the dominant regulator of nuclear stiffness. Cells lacking lamin A/C exhibit more deformable nuclei, with a 50% reduction in stiffness. Conversely, overexpression of lamin A/C increases nuclear stiffness proportionally<sup>[13-15]</sup>. Importantly, the trends agree with the strong positive scaling between nuclear lamin levels and tissue stiffness: lamin A protein levels in the softest tissues, such as brain and marrow, are on average ~30-fold lower than those in stiffer tissues such as cartilage and bone<sup>[13]</sup>. Cells in stiffer, mechanically stressed tissues consequently possess stiffer and stronger nuclei. Lamin B provides baseline structural integrity but cannot compensate for the loss of lamin A/C<sup>[16]</sup>. Cells deficient in lamin A/C or with lamin A/C mutations exhibit severe defects in nuclear stability, cytoskeletal dynamics, and nucleo-cytoskeletal force transmission<sup>[17-19]</sup>. Additionally, these cells are unable to sufficiently activate mechanoresponsive genes upon mechanical stimulation<sup>[20,21]</sup>, highlighting the critical role of the lamina, particularly lamin A/C, in cellular mechanotransduction.

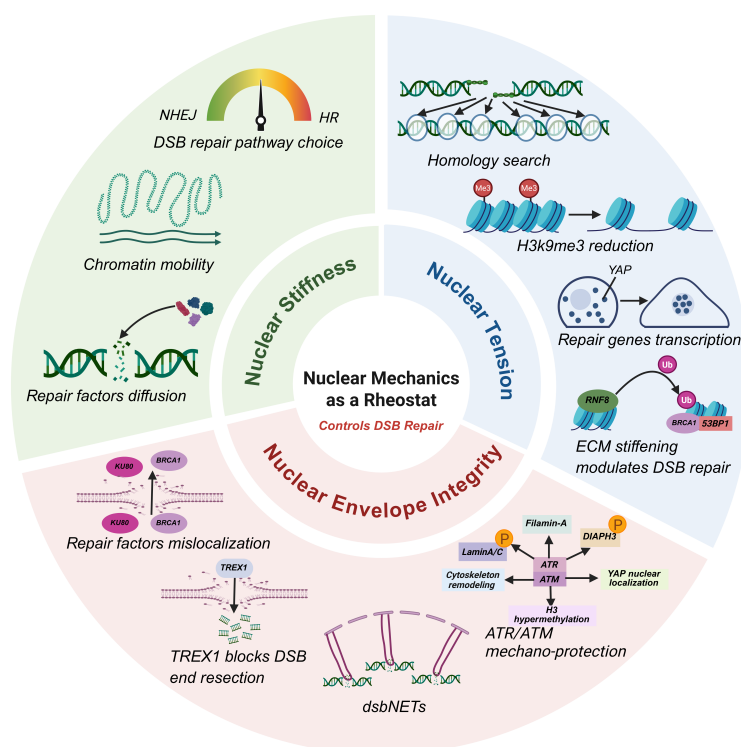
While the lamina serves as the nuclear boundary, the nuclear interior is occupied by chromatin, a DNA-histone polymer network exhibiting viscoelastic gel behavior<sup>[22]</sup>. Chromatin, which exists in nucleosomes and is further organized into euchromatin and heterochromatin, plays a major part in the mechanical strength and deformability of the nucleus<sup>[23,24]</sup>. Heterochromatin, characterized by histone modifications such as H3K9me3 and H3K27me3, is tethered to the nuclear periphery, thereby imparting nuclear stiffness and attenuating chromatin flow. In contrast, euchromatin, marked by histone modifications like H3K9ac or H3K4me3, is untethered and can flow unabated, leading to compromised nuclear stiffness. Loss of heterochromatin causes nuclear softening and abnormal nuclear morphology<sup>[25]</sup>. Treatment with histone deacetylase inhibitors to increase euchromatin or histone methyltransferase inhibitors to decrease heterochromatin results in a softer nucleus, without perturbing lamins. Conversely, an increased content of heterochromatin raises nuclear stiffness by approximately two-fold<sup>[22,26]</sup>. Collectively, chromatin-based nuclear

mechanics are determined by the levels of euchromatin and heterochromatin. Moreover, heterochromatin protein 1 $\alpha$  (HP1 $\alpha$ ), which crosslinks heterochromatin domains, contains a disordered region that acts as a mechanosensitive entropic spring. HP1 $\alpha$ -mediated chromatin crosslinking is essential for nuclear shape maintenance; degradation of this process results in decreased chromatin stiffness and nuclear rigidity<sup>[27]</sup>. Thus, nuclear stiffness can be regulated by modulating the compaction state of chromatin. Furthermore, changes in chromatin compaction and epigenetic state have been observed in response to mechanical cues such as substrate stretching, cell compression, and constricted migration<sup>[26,28,29]</sup>. For instance, exogenous tensile or shear forces on cells cause chromatin decondensation and nuclear softening, altering susceptibility to gene expression changes and even resulting in DNA damage<sup>[26,30]</sup>.

Last but not least, the nucleus is physically tethered to the LINC complex, which is embedded in the nuclear envelope and bridges the cytoplasm with the nucleus, enabling the transduction of extracellular mechanical signals into the nuclear interior. The LINC complex comprises klarsicht, ANC-1, and syne homology (KASH) proteins that anchor within the ONM and sad1-UNC-84 homology (SUN) proteins located on the INM<sup>[31]</sup>. In the perinuclear space, SUN proteins physically bind to the lamina and chromatin. Nuclear envelope spectrin repeats (nesprins), a classical KASH protein, interact with actin, microtubules, or intermediate filaments in the cytoplasm and function as elastic springs and force conduits. Notably, the LINC complex is required for maintaining internal structural stability and governing nuclear stiffness. Deletion of SUN proteins severely impairs nucleo-cytoskeletal force transmission, which is accompanied by changes in chromatin dynamics<sup>[32-34]</sup>.

### 3. Nuclear Mechanics Impacts DNA Damage Repair

The nuclear context in which DNA damage is situated plays a crucial role in determining the selection of repair mechanisms. Having described the contributing components to nuclear mechanics, we will now illustrate how nuclear stiffness, tension, and envelope integrity impact DDR processes (Figure 2).



**Figure 2.** Nuclear mechanics as a rheostat controls DSB repair. Nuclear stiffness, tension, and envelope integrity collectively regulate DSB repair. Nuclear stiffness regulates repair factor diffusion, chromatin mobility, and the NHEJ/HR balance. Nuclear tension, transmitted from ECM stiffening via the cytoskeleton, reduces H3K9me3 levels, promotes YAP nuclear translocation, and affects RNF8-mediated ubiquitination signaling, which in turn modulates DSB repair and homology search. Nuclear envelope integrity is critical for proper localization of repair factors; envelope rupture causes mislocalization of KU80 and BRCA1, allows TREX1 to block DSB end resection, induces dsbNETs formation, and activates ATM/ataxia ATR mechano-protection pathways. ATR preserves nuclear integrity and stiffness by recruiting Filamin-A and phosphorylating DIAPH3 and lamin-A/C to promote nuclear actin polymerization. ATM facilitates DNA repair via cytoskeletal and chromatin remodeling. Both kinases enable mechanical adaptation independently of their canonical DDR signaling roles. Collectively, nuclear mechanics serves as a physical rheostat that tightly controls DSB repair progression. DSB: double-strand break; NHEJ: non-homologous end joining; HR: homologous recombination; ECM: extracellular matrix; YAP: yes-associated protein; KU80: X-ray repair cross-complementing protein 5; BRCA1: breast cancer type 1 susceptibility protein; ATR: ataxia telangiectasia and rad3-related protein; ATM: ataxia telangiectasia mutated; DIAPH3: diaphanous related form 3; dsbNETs: DSB-capturing nuclear envelope tubules; DDR: DNA damage repair; TREX1: three-prime repair exonuclease 1.

### 3.1 Nuclear stiffness underlying DNA damage repair

*Nuclear stiffness regulates DDR factors diffusion.* Upon DNA damage, DDR factors such as the MRN complex and KU70/80 diffuse through the nucleoplasm to recognize DSBs within seconds to minutes, recruiting ataxia-telangiectasia mutated (ATM) or DNA-PKcs to trigger downstream cascades. While the absolute protein concentration of DNA repair factors is a key determinant for the kinetics of DDR proteins recruitment to DNA damage sites, their recruitment is also determined by the effective diffusion coefficient, which is directly suppressed by nuclear stiffness. Chromatin decompaction induced by histone acetylation restores diffusion even with high lamina stiffness, whereas dense heterochromatin creates a tortuous path for macromolecular diffusion, making DSB repair in heterochromatin roughly two-fold slower than in euchromatin<sup>[35,36]</sup>. In line with this, chromatin decondensation leads to more rapid diffusion in the nucleus, resulting in higher accessibility of repair factors and promotes repair efficiency<sup>[37]</sup>. Furthermore, as the cell undergoes nucleus squeezing-induced increase in chromatin density, critical DNA repair factors such as breast cancer type 1 susceptibility protein (BRCA1), X-ray repair cross-complementing protein 5 (KU80) and 53BP1 are significantly depleted, contributing to a delay in DNA damage repair<sup>[38]</sup>.

Beyond regulating the diffusive mobility of repair factors, the local density of chromatin is a primary determinant of the phase equilibrium of droplet-like biomolecular condensates, thereby facilitating vital roles in gene expression and DDR. In dense heterochromatin, enhanced macromolecular crowding lowers the critical concentration required for liquid-liquid phase separation (LLPS), thereby promoting condensate nucleation by concentrating repair factors within a restricted volume<sup>[39]</sup>. Conversely, chromatin decompaction results in reduced nuclear heterogeneity and stiffness, which strongly correlates with impaired growth rates, reduced sizes, and decreased mobility of embedded condensates following phase separation. Interestingly, relaxing the constraints of chromatin at the nuclear boundary by knocking down lamin proteins does not significantly impact overall phase equilibrium, suggesting the nuclear cortex does not affect local condensate equilibria<sup>[40]</sup>. Once assembled, DSB repair foci resemble LLPS around damaged areas while excluding non-repair factors<sup>[41]</sup>. In the context of heterochromatin damage repair, a phase-separated environment is essential for selectively retaining or excluding repair proteins to modulate repair pathway choice and repair progression. For example, the heterochromatin domain may be permeable to resection and checkpoint components, while excluding the NHEJ factor KU80. The strand invasion component RAD51 recombinase (RAD51), and Arp2/3 activators Scar and Wash, may also be excluded, thus enabling resection inside the heterochromatin domain and filament formation at its periphery. Moreover, nuclear actin filaments (F-actin) and myosins drive the directed motion of heterochromatin repair sites to the nuclear periphery<sup>[42]</sup>.

*Nuclear stiffness restricts chromatin mobility.* DDR not only involves the diffusion of repair factors, but also entails chromatin mobility, which has been implicated in DSB relocation, clustering, and homology search needed for HR<sup>[43–46]</sup>. Replication-dependent histone (Repli-Histo) labeling study demonstrates that the nucleosome motion in euchromatic regions is greater than that in heterochromatic regions, presumably due to additional crosslinks in heterochromatin such as heterochromatin protein 1 (HP1) and the lamina. The chromatin motion remains constant throughout interphase<sup>[47]</sup>. Heterochromatic DSBs relocate to the periphery of heterochromatic domains, accompanied by enhanced mobility favoring HR repair<sup>[48–50]</sup>. Chromatin mobility involves coordination with the nuclear lamina, LINC complex, and cytoskeleton. Lamin A/C facilitates the ATM-mediated DDR signaling, including the phosphorylation of H2AX at Ser139 (γH2AX), checkpoint kinase 1 (CHK1) and CHK2<sup>[51]</sup>, and suppresses chromatin dynamics to immobilize broken DNA ends<sup>[52]</sup>. In addition, the actin-nucleating actin-related protein 2/3 complex (ARP2/3) complex specifically increases HR pathway efficiency by clustering DSBs together through nuclear actin polymerization<sup>[53,54]</sup>. Loss of lamin A/C or emerin, affects nuclear myosin 1 (NM1) localization and activity, causing enhanced chromatin mobility toward the nuclear interior<sup>[55]</sup>. Recent studies revealed that intermediate filament family orphan 1 and 2 (IFFO1/2) connect to the lamina to prevent DSB end mobility and promote NHEJ<sup>[56,57]</sup>. Moreover, the 53BP1 physically interacts with the LINC complex, which in turn links to dynamic microtubules. DNA broken ends coated by 53BP1/LINC complex exhibit enhanced mobility, even when situated away from the nuclear periphery, promoting the mis-rejoining by NHEJ in BRCA1-deficient cells<sup>[2]</sup>. Microtubule depolymerizing kinesin, kinesin family member 2A (KIF2A)-mediated nuclear envelope invaginations promote the efficient recruitment of 53BP1-replication timing regulatory factor 1 (RIF1), thereby facilitating NHEJ repair<sup>[58]</sup>. In addition, both actin and microtubule cytoskeletons participate in nuclear mechanotransduction and consequently chromatin mobility. The radius of confinement (Rc), a key parameter determining the effective volume that DNA broken ends can explore, is significantly reduced when actin dynamics are impaired by latrunculin A<sup>[59]</sup>.

*Nuclear stiffness biases DSB repair pathway choice.* The most critical decision in DSB repair is whether to ligate DSB ends directly via NHEJ or resect DSB ends to generate single-stranded overhangs for HR. The balance between NHEJ and HR is largely determined by the antagonistic relationship between 53BP1 and BRCA1<sup>[60]</sup>. It is well established that 53BP1 binds to DSB ends via H4K20me2, and recruits downstream NHEJ factors such as RIF1 and REV7 to inhibit resection<sup>[61,62]</sup>. In addition to traditional biochemistry factors, nuclear stiffness directly regulates DSB repair pathway choice<sup>[63,64]</sup>. Chromatin architecture is now recognized as a crucial determinant of DSB repair. For instance, lesions occurring in euchromatin are preferentially repaired by error-free HR<sup>[65]</sup>, while DSB in heterochromatin need to be relocated to peripheral euchromatin regions, allowing access to repair machinery and enabling HR<sup>[50,66]</sup>. However, for DSBs within lamina-associated domains (LADs), HR is restricted to favour NHEJ<sup>[67]</sup>. Notably, lamin A/C balances and shifts between DSB repair pathways through maintaining the expression of 53BP1, BRCA1, and RAD51<sup>[68]</sup>. On one hand, lamin A/C binds 53BP1 and promotes its nuclear retention and stability. Depletion of lamin A/C not only reduces the global 53BP1 protein level,

but also impairs the formation of 53BP1 ionizing radiation (IR)-induced foci (IRIF), thereby compromising NHEJ<sup>[63,69]</sup>. On the other hand, lamin A/C transcriptionally regulates the BRCA1 and RAD51. Mechanistically, loss of lamin A/C promotes the assembly of the transcriptional repressor complex p130/E2F4, which binds to E2F sites in the BRCA1 and RAD51 promoters, leading to decreased protein levels of both BRCA1 and RAD51, as well as diminished RAD51 IRIF formation<sup>[64,68,70,71]</sup>. Similarly, lamin B1 binds to key repair proteins such as 53BP1 and RAD51. Lamin B1 modulates HR by maintaining RAD51 stability through inhibiting proteasome-mediated degradation<sup>[72]</sup>. Influenced by microtubule dynamics, lamin B1 forms tubules that push chromatin aside and closely associate with ATM and DNA-PKcs. These lamin B1 tubules facilitate the coordination and repair of DSBs by enabling rapid resolution of nearby 53BP1-marked DSBs<sup>[73]</sup>. Yet, lamin B1 overexpression directly binds and sequesters 53BP1, thereby impeding DSB repair. Lamin B1 also modulates HR repair through regulating the expression of essential genes such as BRCA1 and MRE11<sup>[74]</sup>. Moreover, the LINC complex has been shown to regulate the pathway choice upon DSB formation. For instance, SUN1 interacts with the KU70/80 heterodimer and DNA-PKcs, driving the inhibition of NHEJ, promoting RAD51 loading at DSBs, and consequently shifting the balance towards HR rather than NHEJ<sup>[75]</sup>.

### 3.2 Nuclear tension underlying DNA damage repair

Nuclear tension, different from stiffness, which resists nuclear deformation, is an active force pulling on the nucleus. Transmitted from the cytoskeleton through the LINC complex and sensed by nuclear envelope proteins, tension influences nuclear plasticity, nuclear envelope dynamics, chromatin organization, and genome integrity<sup>[76-78]</sup>. Unlike stiffness, which changes over hours, tension can be modulated in seconds, acting as a fast mechanical switch that regulates DNA repair pathway choice, dominating short-term regulation while stiffness sets the baseline<sup>[79,80]</sup>. Critically, during nuclear migration, increased tension not only triggers more DNA damage, but also inhibits HR repair by reducing the contact between the centromere-proximal chromatin and the adjacent chromosome arm<sup>[81]</sup>. Emerin, an INM protein, mediates bridging between the cytoskeleton and heterochromatin via translocation between the INM and ONM. In response to increased nuclear tension, emerin undergoes conformational changes and tyrosine phosphorylation<sup>[79,82,83]</sup>. Biaxial strain assays have shown that emerin-deficient fibroblasts exhibit normal nuclear deformation but abnormal morphology and impaired mechanosensitive gene expression<sup>[84]</sup>, whereas micropipette aspiration has revealed a reduced ratio of the area expansion to shear moduli ( $K/\mu$ ) in emerin-deficient nuclei, suggesting altered nuclear envelope elastic properties<sup>[85]</sup>. These discordant findings indicate that emerin's mechanical contribution varies with cellular context and measurement modality. Nevertheless, emerin deficiency consistently impairs LAD-associated heterochromatin release, thereby reducing DDR gene accessibility under stretch- or strain-induced nuclear tension<sup>[86]</sup>. Extensive nuclear deformation during confined migration can cause nuclear envelope rupture, replication stress, DNA damage, and heterochromatin formation, which in turn alters chromatin accessibility<sup>[87-89]</sup>. Notably, NHEJ has recently been identified as the primary repair mechanism for migration-induced DSBs, which arise from topoisomerase II $\beta$  covalently bound intermediates in neuronal cells. Treatment with inhibitors targeting key NHEJ components, LIG4 and DNA-PKcs, disrupted the resolution of  $\gamma$ H2AX foci following migration through 3  $\mu$ m pores, yet had no apparent effect after migration through 8  $\mu$ m pores. In contrast, inhibition of the HR pathway using a RAD51 inhibitor exerted minimal impact on  $\gamma$ H2AX focus formation or resolution. Although DNA-PKcs is a mechanosensitive DDR kinase implicated in NE tubule formation<sup>[90]</sup>, inhibition of DNA-PKcs did not affect NE invagination after transwell migration, suggesting that the DSB repair defect stems from impaired NHEJ rather than from altered NE morphology<sup>[91]</sup>. Moreover, stretch-induced nuclear deformation exhibits H3K9me3 reduction, leading to chromatin softening and nuclear envelope disintegration, both of which exacerbate DNA damage<sup>[26]</sup>.

Mechanical cues from extracellular matrix (ECM) modulate nuclear morphology. The stiffness of the ECM functions upstream of nuclear tension, and is critical for understanding cellular mechanics and their implications for genomic stability. As ECM stiffness increases, actomyosin contractility rises, imposing additional mechanical stress on the nucleus and creating conditions that predispose it to rupture. Cells sense ECM stiffness through integrins and transduce this signal into actomyosin contractility via the ras homolog gene family member A (RhoA)/Rho-associated protein kinase (ROCK) pathway. On rigid substrates, stress fibers assemble to engage adhesions, applying tension and compression to the nucleus. This further elevates nuclear tension and increases nuclear curvature, correlating with more frequent nuclear ruptures, especially in cells with compromised nuclear integrity. Conversely, soft matrices maintain low nuclear tension. ECM stiffness-induced nuclear tension regulates gene expression by modulating yes-associated protein (YAP) cytoplasmic-nuclear translocation. Knockdown of lamin A/C abolishes nuclear tension and reduces nuclear YAP localization<sup>[92]</sup>. Extracellular mechanical cues influence DNA repair by activating the hippo kinases MAP4K4/6/7, which phosphorylate ubiquitin on soft matrices, impairing RNF8-mediated ubiquitin signaling at DSB sites and leading to deficient recruitment of BRCA1 and 53BP1, thereby impairing DSB repair<sup>[93]</sup>.

### 3.3 Nuclear envelope integrity underlying DNA damage repair

The NE is a double-layered membrane that shields the genomic DNA within the nucleus and maintains nuclear structural integrity, primarily through lamina proteins. The NE also functions as a mechanosensing hub, transmitting mechanical forces from the extracellular environment via the LINC complex<sup>[94]</sup>. When cells migrate through confined spaces or experience excessive compression, the nuclear envelope temporarily loses its barrier function, resulting in NE rupture, a catastrophic mechanical failure that compromises the physical separation between the genome and the cytoplasm<sup>[95]</sup>. In general, lamin A deficiency exacerbates

frequent NE rupture, causing mislocalization of cytoplasmic and nuclear proteins, translocation of organelles into the nucleus, genomic DNA leakage into the cytoplasm, activation of inflammatory pathways, and significant DNA damage<sup>[96,97]</sup>.

DDR relies heavily on the availability of relevant repair factors within the nucleus. However, NE rupture leads to mislocalization of various DNA repair factors, including KU80 and BRCA1, leading to increased DNA damage<sup>[98]</sup>. Overexpression of KU70/80 and BRCA1 can restore the DNA damage level back to normal<sup>[99]</sup>. Alternatively, it is also plausible that the increase in DNA damage level is caused by compaction of the chromatin and segregation of nuclear factors away from the chromatin<sup>[38]</sup>, analogous to liquid being squeezed out of a compressed sponge. Consequently, more DNA damage might be expected during migration through denser collagen matrices of stiffer tissues, which could explain the higher mutational load in tumors of stiff tissues. Furthermore, NE rupture allows cytosolic nucleases like three-prime repair exonuclease 1 (TREX1) to enter the nucleus and degrade exposed DNA, blocking DSB end resection and shifting repair toward error-prone NHEJ<sup>[99]</sup>. Notably, the nuclear envelope at the nuclear periphery is enriched in the protein nuclear membrane endonuclease-exonuclease (NUMEN), which promotes NHEJ and limits HR by generating short 5' overhangs at damage sites, while the formation of DSB-capturing nuclear envelope tubules (dsbNETs) facilitates DSB repair and improves cell survival<sup>[100]</sup>.

Mechanical compression and confined migration induce nuclear deformation and elicit cytoskeletal changes<sup>[101,102]</sup>. Distinct from their canonical functions in DDR signaling, ATM and ataxia telangiectasia and rad3-related protein (ATR) kinases respond to mechanical stress at the nuclear envelope and are essential for preserving nuclear integrity and mechanics<sup>[78,80]</sup>. ATR responds to mechanical stress at the NE. ATR is activated by nuclear compression, maintains nuclear integrity and elasticity, and drives nuclear actin assembly via Filamin-A recruitment to the INM through ras association domain family member 1 isoform A (RASSF1A)<sup>[103]</sup>. During NE rupture, ATR regulates nuclear stiffness by phosphorylating formins, diaphanous related formin 3 (DIAPH3) at Ser1072, thereby promoting nuclear actin polymerization<sup>[104]</sup>. ATR has also been linked to DNA damage-induced NE rupture through phosphorylation of lamin-A/C<sup>[105]</sup>. Conversely, ATM is activated by stretching and compression during interstitial migration, modulating the cytoskeleton and chromatin remodeling to facilitate efficient DNA repair. ATM deficiency leads to nuclear YAP localization, nuclear fragmentation, cytoskeletal alterations, and increased H3 hypermethylation, while ATR deficiency results in loss of nuclear stiffness, cytoplasmic YAP accumulation, NE invagination and rupture, and formation of perinuclear cGAS foci following nuclear compression<sup>[106]</sup>. Both kinases enable cellular adaptation to mechanical stress through complementary mechanisms separate from their canonical DDR roles.

### 3.4 Bidirectional interplay: How the DDR remodels nuclear mechanics

Beyond the well-established effect of nuclear mechanics on DDR efficiency, emerging evidence indicates that the DDR actively feeds back to modulate nuclear mechanical properties. Using atomic force microscopy, cisplatin-treated cell nuclei exhibited a significant stiffness reduction, an effect correlated with global chromatin decondensation and attenuated by ATM inhibition, indicating that nuclear softening arises from downstream DDR signaling rather than from physical DNA lesions alone<sup>[107]</sup>. Chromatin architecture serves as a primary determinant of nuclear stiffness. Of note, following DNA damage, chromatin dynamics are temporally and spatially regulated. DSBs induce local chromatin decondensation and increased mobility at 53BP1-labeled damage sites, a process associated with transcriptional repression of nearby genes and facilitation of repair<sup>[108]</sup>. This localized decondensation reduces chromatin density and thereby decreases local nuclear stiffness, creating a permissive environment for repair factor mobility. As discussed, H3K9me3-enriched heterochromatin regions may impede repair factor access, leading to delayed or inefficient repair. Conversely, DSBs trigger the rapid recruitment of histone methyltransferases (HMTs) that deposit H3K9me3 at damage sites, facilitating the recruitment and activity of repair factors<sup>[88,109]</sup>. Histone modifications are critical for regulating both chromatin-based nuclear stiffness and repair efficiency. This intricate crosstalk establishes that nuclear stiffness is not a static material property but a dynamically regulated parameter, governed by the equilibrium of chromatin-modifying enzymes that either loosen or compact the genome in response to DNA damage.

DNA damage can also directly compromise nuclear envelope integrity through modification of the nuclear lamina. Genotoxic stress activates ATR-dependent phosphorylation of lamin A/C, alters lamina assembly, and ultimately induces nuclear envelope rupture in the absence of an externally imposed mechanical challenge. Cancer cells with intrinsic DNA repair defects display particularly frequent DNA damage-induced rupture events, indicating that persistent endogenous DNA damage can generate an acquired nuclear envelope vulnerability. This mechanism provides direct evidence that DDR signaling modifies a core structural determinant of nuclear stiffness and envelope stability<sup>[105]</sup>. The consequences of DDR-induced mechanical remodeling are likely context-dependent, varying with their magnitude, duration, and cellular context. Transient chromatin decondensation and nuclear softening may increase intranuclear protein mobility and facilitate repair, whereas sustained lamina disorganization and recurrent nuclear envelope rupture may aggravate genome instability. Thus, an initially adaptive mechanical response may become detrimental when DNA damage persists or nuclear envelope repair is incomplete. Collectively, current evidence supports a feedback loop in which DDR signaling remodels chromatin-based nuclear stiffness and nuclear envelope integrity. A corresponding feedback regulation of nuclear tension is also suggested, but remains less well defined. Determining the temporal sequence, reversibility, and cellular context of these changes will be necessary to establish when DDR-induced mechanical remodeling promotes repair and when it instead

contributes to persistent DNA damage and genomic instability.

#### 4. Nuclear Mechanics Abnormalities in Aging and Cancer

**Aging.** Mechanical stress can compromise the nucleus's capacity to withstand pressure, thereby driving cellular senescence. Central to this structural resilience are the lamin proteins, particularly lamin A/C and lamin B1, whose downregulation serves as a prominent hallmark of senescence. Notably, persistent lamin A/C-deficient alveolar macrophages exhibit constitutive nuclear envelope rupture, DNA damage, and p53-dependent senescence<sup>[110]</sup>. Mechanical forces that weaken the nucleus further exacerbate senescence, a process in which the YAP/PDZ-binding motif (TAZ) signaling axis plays a pivotal protective role. In younger cells, YAP/TAZ activity suppresses the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase–stimulator of interferon genes (cGAS-STING) pathway, by transducing mechanical signals into appropriate cellular outputs. However, with advancing age, declining YAP/TAZ activity permits spontaneous activation of cGAS-STING, thereby fueling inflammaging<sup>[111,112]</sup>. A major contributor to this aberrant activation is the age-related loss of heterochromatin, which heightens genomic vulnerability to DNA damage and promotes senescence. This heterochromatin decline is particularly pronounced in stromal and contractile cells, suggesting that aging-related dysfunction may originate in these populations. Consequently, preserving heterochromatin architecture and nuclear integrity is essential to forestall premature cellular aging induced by both DNA damage and mechanical stress<sup>[113]</sup>.

**Cancer.** In the case of cancer, the nucleus exhibits aberrant size, volume, and shape, which are classic features in diagnostic and staging procedures. Altered expression of nuclear lamins, particularly lamin A/C, has been postulated to cause nuclear shape changes during cancer progression<sup>[114,115]</sup>. Tumor cells are constantly exposed to compressive forces generated within the tumor microenvironment or during metastatic migration across vascular barriers, and such nuclear compression can cause nuclear envelope breaks, especially in mechanically fragile nuclei<sup>[116]</sup>. Solid tumors often exhibit increased matrix stiffness due to desmoplasia and fibrosis, which is transmitted to cancer cell nuclei, elevating nuclear stiffness and leading to increased mutagenesis, translocations, genomic instability, and driving tumor evolution<sup>[117]</sup>. Notably, nuclear stiffness plays a crucial role in cancer cells migration. Metastatic cancer cells often downregulate lamin A/C to soften their nuclei for efficient migration through narrow tissue confinements. For instance, highly metastatic prostate cancer cells PC-3 have a nuclear stiffness of approximately 0.4 kPa, moderately metastatic prostate cancer cells DU-145 display a nuclear stiffness of around 4 kPa, and normal prostate cells RWPE1 possess a nuclear stiffness of around 6.5 kPa<sup>[118]</sup>. This mechanical softening may explain why metastatic tumors are sometimes more chemosensitive than primary tumors.

Beyond these cell-intrinsic mechanical alterations, solid tumors often exhibit a multifaceted and heterogeneous mechanical landscape *in vivo*, characterized by ECM stiffening, elevated interstitial pressure, and abnormal hemodynamic forces<sup>[119]</sup>. In particular, the ECM stiffness heterogeneity manifests across multiple dimensions, between tumor types, across regions within the same tumor, and over time. For example, pancreatic tumors display an exceptionally dense desmoplasia with pronounced stiffness (10–100 kPa) and solid stress<sup>[120,121]</sup>, while triple-negative breast cancer exhibits a more heterogeneous mechanical landscape, with stiff regions (~140 kPa) coexisting with softer, more invasive zones<sup>[122]</sup>. Hepatocellular carcinoma ranges from 2–20 kPa, while colorectal cancer shows stage-dependent stiffness from 3–14 kPa<sup>[123]</sup>. Glioblastoma displays viscoelastic heterogeneity, wherein softer niches preserve stem-like phenotypes and stiffer matrices promote proliferative or mesenchymal phenotypes<sup>[124]</sup>. Furthermore, within individual tumors, ECM stiffness exhibits pronounced spatial gradients. The tumor core is typically characterized by the densest and most crosslinked matrix, while the invasive margin exhibits distinct collagen alignment and intermediate stiffness that facilitates invasion<sup>[125]</sup>. This regional stiffness gradient directly guides migratory trajectories and impacts drug penetration and immune cell infiltration<sup>[126]</sup>. Moreover, therapeutic interventions exert bidirectional and dynamic effects on ECM mechanics. Chemotherapy can transiently relieve stiffness through tumor debulking, yet therapy-activated cancer-associated fibroblasts (CAFs) may paradoxically induce collagen crosslinking and secondary stiffening, promoting chemoresistance. Radiotherapy elicits biphasic responses, acute softening followed by transforming growth factor- $\beta$  (TGF- $\beta$ )-driven fibrotic stiffening that re-establishes immune exclusion barriers<sup>[127]</sup>. These therapy-induced mechanical dynamics collectively generate a “mechano-resistant” niche.

**Therapeutic Opportunities and Challenges.** Targeting DNA damage repair pathways holds promise for delaying the onset of cancer and promoting therapeutic outcomes. Given the importance of nuclear mechanics in DDR regulation, the nuclear mechanical abnormalities in cancer, such as lamin A/C dysregulation, chromatin structure alteration, and increased rupture frequency, offer new therapeutic avenues. Manipulating the nuclear mechanical properties of tumor cells can alter DNA damage repair outcomes and improve the efficacy of tumor therapeutics. For instance, nuclear softening via lamin A/C knockdown impairs DNA repair<sup>[128]</sup>, promising for sensitizing tumors to DNA-damaging agents. In BRCA1-deficient cells, lamin A/C depletion increases nuclear envelope invagination, enhances DSB mobility, promotes chromosomal aberrations, and potentiates poly (ADP-ribose) polymerase (PARP) inhibitor cytotoxicity<sup>[129]</sup>. Similarly, lamin A/C-deficient cells show heightened sensitivity to interstrand crosslinking agents, including cisplatin, camptothecin, and mitomycin<sup>[128]</sup>. Histone deacetylases (HDACs) inhibitor-mediated chromatin decondensation has been shown to reduce nuclear stiffness in human mesenchymal stem cells, an effect independent of lamin expression<sup>[130]</sup>. Although HDAC inhibitors are well established to sensitize tumor cells to chemotherapy through suppression of DNA repair, including impaired  $\gamma$ H2AX foci resolution and reduced expression of BRCA1 and RAD51<sup>[131,132]</sup>, direct evidence linking histone deacetylase inhibitors

(HDACi)-induced nuclear softening to compromised DNA repair in tumors remains lacking. Nevertheless, the established radiosensitizing and chemosensitizing effects of HDAC inhibitors in head and neck and breast cancers support their clinical investigation as adjuncts to chemotherapies<sup>[133]</sup>. Beyond direct nuclear targeting, stroma-normalizing agents that reduce ECM stiffness and solid stress improve drug penetration while mitigating mechanically induced DNA damage<sup>[134-136]</sup>.

Thus, combination therapies that integrate biomechanical interventions with chemotherapy, radiotherapy, and immunotherapy offer a more comprehensive therapeutic approach. Fasudil-mediated ROCK inhibition enhances pancreatic tumor chemosensitivity by disrupting ECM integrity, reducing matrix stiffness, improving vascular perfusion, and drug delivery<sup>[137]</sup>. Additionally, hyaluronidase-induced degradation of tumor stromal hyaluronic acid (HA), a major ECM component, enhances radiosensitivity and chemosensitivity in preclinical studies<sup>[138-140]</sup>. Preclinical studies in selected tumor models suggest that YAP/TAZ inhibition may improve T-cell activity or enhance immune checkpoint blockade; whether it can benefit adoptive T-cell therapy in pancreatic cancer remains to be determined<sup>[141-143]</sup>. Collectively, these findings suggest that biomechanical targeting combined with conventional therapies represents a promising strategy to overcome treatment resistance and improve clinical outcomes.

## 5. Conclusions and Future Perspectives

In conjunction with classic biochemical pathways, nuclear mechanics, including stiffness, tension, and envelope integrity, profoundly impact DDR by controlling the diffusion and recruitment of repair factors, DNA end mobility, and repair pathway choice. Nonetheless, several key questions remain unresolved. Future studies are needed to elucidate the detailed molecular mechanisms through which cells temporally and spatially coordinate DDR with dynamic changes in nuclear mechanics. Furthermore, future research should address the impact of three-dimensional tumor architecture and solid stress on nuclear mechanics *in vivo*, determine whether nuclear mechanical properties can serve as predictive biomarkers for cancer therapy outcomes, and develop innovative mechano-pharmacological strategies that selectively target cancer cells based on their mechanical vulnerabilities.

## Declarations

### Authors contribution

Ma X, Guo C: Conceptualization, writing-review & editing.  
Zhai P, Cheng Z, Feng Y, Cui Y, Wang D: Writing-original draft.

### Conflicts of interest

The authors declare 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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