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Living under Strain: How Epithelia Protect Their Genomes from Repeated Stretching

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Cells sense and respond to the mechanical properties of their surrounding microenvironment. Morphogenesis and maintenance of epithelial tissues rely on force-transmission machinery that indirectly tethers the nucleus to the extracellular matrix (ECM) and allows for bidirectional crosstalk between the microenvironment around a cell and its center for decision-making. Whether it be shear stress on endothelial cells due to blood flow or the stretching of lung tissue with each breath, epithelial tissues experience a variety of mechanical stresses and have evolved to alleviate potentially harmful mechanical effects on the genome of their constituent cells. Failure to do so could lead to genomic instability, a hallmark of cancer, in part due to double-stranded breaks in the DNA or mutations that result from their misrepair. A recent paper from Nava et al. describes novel mechanisms by which chromatin, compact packages of DNA molecules, is protected from DNA damage following stretch-induced nuclear deformation.[1] The authors use a powerful combination of RNA- and ChIP-sequencing, proteomics, and high-resolution imaging to characterize the short- and long-term strategies employed by epithelial cells to mitigate the effects of nuclear deformation, which could otherwise jeopardize genomic stability.

Eukaryotic DNA is coiled around histone proteins to form relatively dense and compact *heterochromatin* or loose *euchromatin*. Heterochromatin is mainly found at the nuclear periphery where, in addition to packing the DNA efficiently, it silences gene expression in part due to post-translational modifications of histones at repeat-rich telomeric or centromeric regions.[2] An example is trimethylation of histone H3 on lysine-9 (H3K9me3), required to anchor heterochromatin to the nuclear lamina, a dense meshwork of filamentous lamin proteins on the inner surface of the nuclear envelope[2] (Figure 1A). Lamins and heterochromatin make the nucleus the stiffest organelle. Previous work demonstrated that squeezing through tiny pores during cell migration requires nuclear deformability and suggested that nuclear softening through decreased expression of lamin-A speeds up cancer cell migration by making it easier for cells to squeeze through tiny pores.[3] The study from Nava et al. demonstrates that epidermal stem/progenitor cells (EPCs) that express high levels of lamin-A respond to stretch-induced nuclear deformation by weakening chromatin−lamina interactions to transiently "soften" their nuclei, which protects their genome. By using super-resolution imaging and tracking CRISPR rainbow-labeled telomeres, the authors show that cyclic stretch reduces H3K9me3 and increases both nuclear wrinkling and chromatin mobility. Specifically, the sudden deformation of the nucleus triggers a rapid flow of Ca^{2+} from the endoplasmic reticulum through the mechanosensitive ion channel Piezo-1 into the cytoplasm, which reduces lamina-associated H3K9me3 heterochromatin, decreases tension on the nuclear envelope to cause wrinkling, and enables mobility of heterochromatin that is no longer attached to the nuclear periphery (Figure 1B,C). This self-defense mechanism takes place in cells with a stiff and taut nuclear envelope, an outcome of high lamin-A expression, and transiently protects the genome from double-stranded breaks. In the meantime, the epithelial sheet reorients itself at the supracellular level and reorganizes its cytoskeleton by aligning F-actin stress fibers in the direction orthogonal to strain. This serves as a long-term strategy in case high-amplitude strain persists and helps prevent the propagation of mechanical stress to the nucleus (Figure 1D).

Importantly, the decrease in H3K9me3 heterochromatin is observed only in cells that express high levels of lamin-A. The authors demonstrate that cancer cells with inherently low levels of lamin-A avoid chromatin remodeling, a feature that could make them prone to DNA damage as a result of mechanical stretching and fuel further genomic instability. Consistently, ectopic expression of lamin-A stiffens the nuclei of cancer cells and sensitizes them to H3K9me3-mediated mechanoprotection. This finding is in line with previous work, which demonstrated that nuclear rupture and DNA damage result from nuclear deformation in cells that express low levels of lamin-A.[4,5] These data also suggest a previously unknown mechanism by which healthy epithelia with stiff nuclei and high lamin-A expression can prevent DNA damage.

Since regions of high H3K9me3 are generally associated with low transcriptional activity, a decrease in its levels could be an indication of altered gene expression. An overlap of ChIP- and RNA-sequencing analysis, however, revealed that decreased H3K9me3 has little transcriptional consequence in the short term, as increased chromatin mobility is observed in

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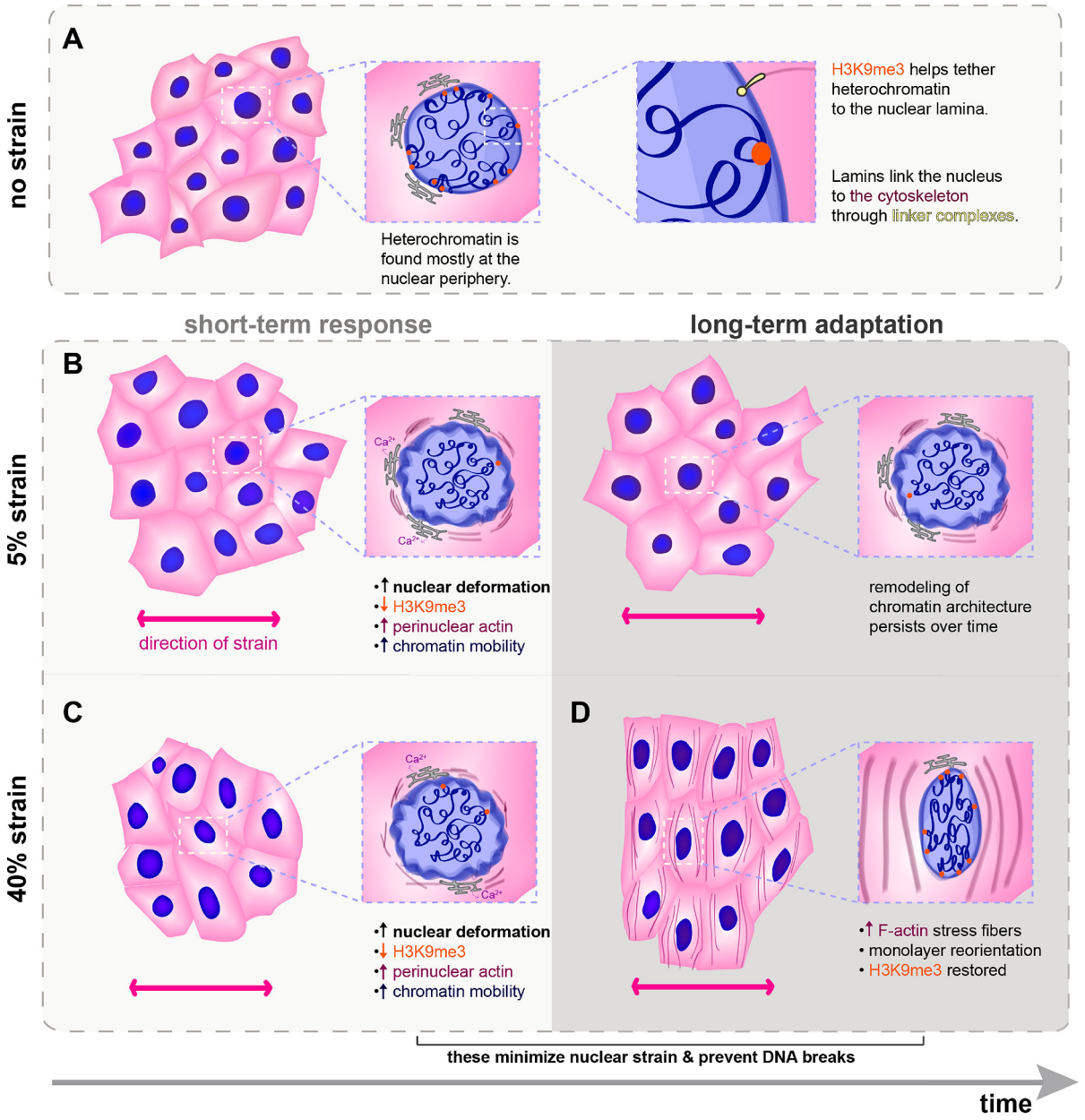

Figure 1. The mechanical microenvironment governs the interactions between nuclear lamina and chromatin to regulate genomic stability. (A) In unstretched cells, heterochromatin is tethered in some places to the mechanosensitive nuclear lamina through histone modifications. Stretching of the epithelium deforms the nuclear envelope and triggers a rapid response that involves an outflow of Ca^{2+} from the ER and then a decrease in H3K9me3 through increased chromatin mobility in cells that experience both (B) low or (C) high strain to prevent DNA breaks. The stretch-induced increase in cytosolic Ca^{2+} is correlated with a decrease in H3K9me3; however, the exact mechanism that connects these two is unclear. In the long term, chromatin remodeling persists in cells under low-amplitude strain, whereas (D) high-amplitude strain leads to an adaptive response that involves cytoskeletal and supracellular rearrangements to prevent the propagation of strain to the nucleus and to restore chromatin architecture.

noncoding regions. Instead, reducing H3K9me3 coverage of telomeric tips of heterochromatin that span noncoding regions transiently turns off nuclear mechanosensing to minimize DNA damage due to the strain on the nucleus. If strain persists in the long term, chromatin remodeling has the potential to alter gene expression and affect lineage specification. Nava et al. demonstrate that EPCs that experience low-amplitude cyclical stretch reduce H3K9me3 heterochromatin similar to their counterparts under high-amplitude stretch, but that long-term mechanoprotection is not initiated even if mechanical stretching persists. Further work is required to determine if these permanent alterations in chromatin architecture could eventually trigger changes in cell identity.

The novel self-defense mechanism uncovered by Nava et al. reveals how tissue-specific stem cells rapidly respond to changes in the mechanical properties of their local microenvironment and protect their genomic integrity by transiently insulating the DNA from mechanical stress. Many tissues, including the lung, stiffen during embryonic development. While low expression of lamin-A could facilitate cellular motility required during morphogenesis, tissue stiffening and a consequent increase in the expression of lamin-A might protect

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healthy epithelial cells from DNA damage downstream of cyclic stretch in fully developed tissues. The work highlighted here provides an elegant description of how nuclear mechanosensing protects the genome of healthy epithelial cells. Future work is required to uncover the molecular mechanisms that enable chromatin remodeling to prevent DNA damage in stretched epithelia. Considering that cancer cells can migrate at the expense of losing genomic stability, this also raises the question of whether defects in this mechanoprotection pathway could lead to carcinogenesis.

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Notes

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ABBREVIATIONS

ECM, extracellular matrix; EPC, epidermal stem/progenitor cell; H3K9me3, trimethylation of histone H3 on lysine-9

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