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► **To cite this version:**

Albano C Meli. Genome protection on the move. Cardiovascular Research, 2020, 116 (10), pp.e109-e111. 10.1093/cvr/cvaa189. hal-02907181

HAL Id: hal-02907181

<https://hal.science/hal-02907181>

Submitted on 29 Jul 2021

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Genome protection on the move

Albano C. Meli *

PhyMedExp, INSERM, CNRS, University of Montpellier, CHU Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France

Keywords Chromatin • Nucleus • Epigenetics • Mechanoprotection

Online publish-ahead-of-print 20 July 2020

This commentary refers to ‘Heterochromatin-driven nuclear softening protects the genome against mechanical stress-induced damage’, by Nava *et al.*, *Cell*, 2020.¹

Functional integrity is essential to maintain physiological homeostasis. Some of the cellular and tissue stress is physiological (e.g. stretching), but in some cases, there are real pathophysiological burdens (e.g. chemical stress or irradiation). DNA damage can lead to genome instability and diseases affecting development and cancers. Therefore, it is vital to shield the nuclear DNA. Many tissues and organs have specific stem cells that are chronically exposed to stretching and/or compression, which are presumably some of the main mechanical signals that could affect not only cellular organelles, but also the genome. How the genome is protected in these cells and what kind of adaptive mechanisms are applied remain unknown.

A recent study by Nava *et al.* addressed these questions in a paper published in *Cell*. They exposed skin epidermis stem/progenitor cells and mesenchymal stem cells to physiological stretch found in the tissues using a device inducing continuous cyclic stretch. They revealed two distinct mechanisms by which cells ensure chromatin mechanoprotection. The first mechanism discovered is a novel, rapid, and sensitive heterochromatin response that involves calcium release from the endoplasmic reticulum to increase chromatin mobility by reducing contact with the nuclear lamina network that underlies the inner nuclear membrane and controls the nuclear architecture. Consequently, the lamina-associated epigenetic modification called Histone 3 lysine 9 trimethylation (H3K9me3) is reduced and the nuclear membrane tension lower.¹ Thus, the nucleus and DNA change their mechanical features and become softer.

The authors observed a second supracellular mechanism of adaptation when the mechanical stress persists. This time, it involves a slower and less sensitive tissue-level reorganization triggered by cell to cell contacts in order to adjust the mechanical energy and reduce force transmission to the nucleus without damaging the genome. In this way, the tissue-level orientation is suitable and adaptive for long-term mechanoprotection.

The authors then addressed whether cancer cells, which are characterized by genome instability and frequent acquisition of mutations, display similar features upon stretch. When compared to healthy stem cells, cancer cells exhibited lower nuclear lamina A levels and elastic moduli as well as a slight increase in H3K9me3 levels upon the stretch. All these features might lead cancer cells to be insensitive to extrinsic

signals, allowing them to escape tissue regulations and become anarchic cells.

Various organs adapt and respond to mechanical forces. Stretch and compression are physiological stresses in the cardiovascular system. The cardiac excitation–contraction coupling transduces the electrical impulses to cardiac muscle contraction for each heartbeat. Therefore, cardiomyocytes need to protect their nuclear material through the entire life. Mutations in the lamin A/C gene (LMNA), among the laminopathies, cause cardiac and skeletal myopathies, including dilated cardiomyopathy. Locations of the mutations affect the nuclear lamin network and are associated with different clinical outcomes.² It is likely that mutated lamin proteins impair the mechanoprotection of the chromatin through dysfunction of the nuclear lamina network since mice deficient in nuclear lamins exhibit marked defects of shape and size with central displacement and fragmentation of heterochromatin, and even with sexual dimorphism.³ In vessels, the dynamic mechanical response of the smooth muscle cells is important to modulate the arterial diameter and resistance. There, lamin mutations have been associated with lipodystrophic syndrome, atherosclerosis, metabolic disturbances, and premature pathological ageing process (progeria) as lamin mutants alter the nuclear structure and stiffness. Consequently, vascular smooth muscle cells are more affected by mechanical stress.⁴

Epigenetic modifications control gene expression and chromatin architecture. The H3K9me3-marked chromatin displays condensed structure that has been reported to constrain gene activity during phylogenic embryonic development and ensure accurate cell identity.⁵ Inhibition of H3K9me3 in adult hearts maintains the cell cycle in cardiomyocytes and causes proliferation and hyperplastic growth,⁶ a pathological feature that can evolve towards hypertrophic cardiomyopathy. Histone trimethylation via H3K9me3 was also found to be repressed and induced overexpression of cardiomyogenesis-related genes and cardiac dysplasia in foetal mice as a model of alcohol-induced congenital heart disease.⁷ In endothelial cells, the oscillatory shear stress implies the acetylation of Histone 3 at lysine 27 (H3K27ac) of the chromatin remodelling. Such epigenetic modifications might be an expanded mechanism leading to the pathogenesis of atherosclerotic plaques.⁸ In mice with type 2 diabetes, a decrease in trimethylation of H3K9 enhances inflammation through pro-inflammatory gene expression in vascular smooth muscle cells.⁹ In both type 1 and 2 diabetes, the glucose transporter GLUT4 expression is reduced. The increase of H3K9me3 modification in the promoter of the *Slc2a4* gene inhibits its expression and therefore that of the GLUT4

* Corresponding author. E-mail: albano.meli@inserm.fr

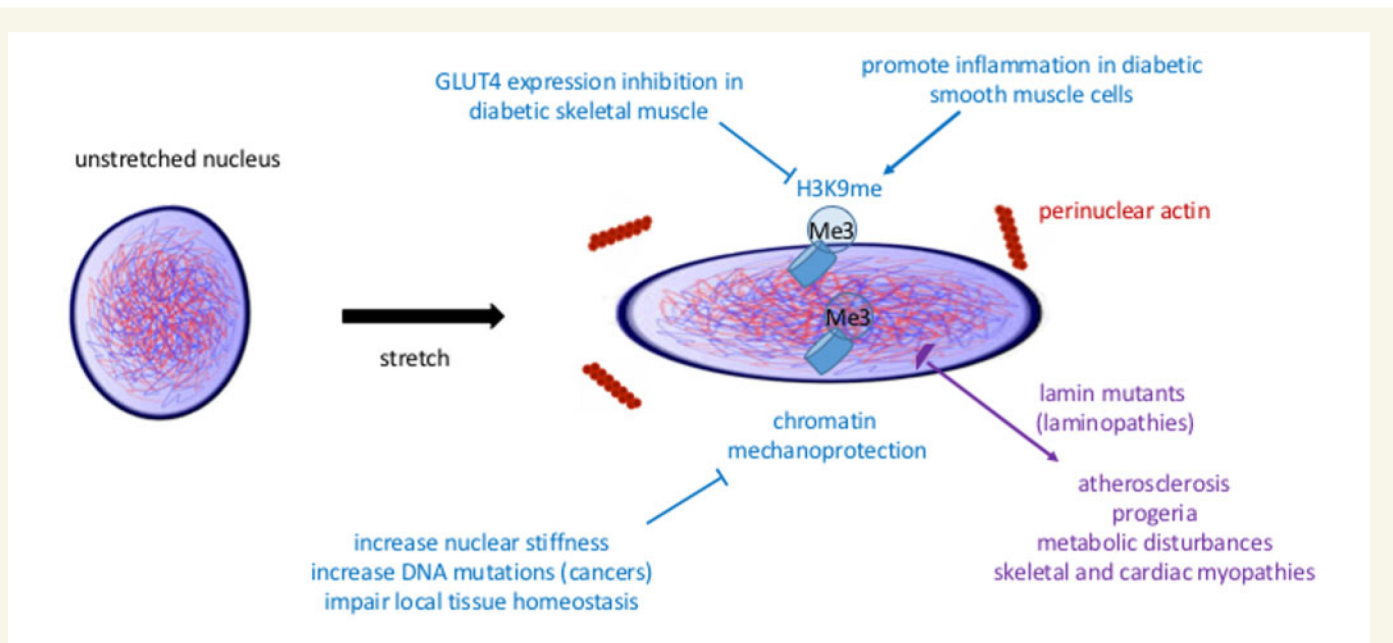


Figure 1 Overview figure summarizing some of the main findings.

protein. This mechanism points out a potential therapeutic target in H3K9me3 for treating diabetes.

In 2016, a major study explored the mechanotransducer role of the cell nucleus in damaged tissue with induced inflammation. The authors found that nuclear swelling and membrane stretch activates inflammatory eicosanoid synthesis via the phospholipase A2 (cPLA₂), arachidonate 5-lipoxygenase (5-LOX), actin filaments, and lamina network to attract leucocytes where the cells are damaged.¹⁰ A process by which lipid bilayer stretch and calcium activate all these actors. The present findings by Nava *et al.* provide some complementary molecular mechanisms to explain the nuclear stretch adaptation for rapid and slower cellular and tissue mechanoresponses (Figure 1). Their model has many biological implications. It can certainly be applied to a broad range of cell and tissue types to further understand how the nuclear stretch sensing is regulated in healthy and pathological conditions. Their findings also point out that dysregulations of histone epigenetic modifications contribute in protecting the chromatin with a fragile balance that can turn towards the development of diseases. These studies make important moves to improving our understanding of this balance.

Conflict of interest: none declared.

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Author



Biography: Albano C. Meli received his PhD in Neurobiology at the Faculty of Pharmacy in Montpellier (France) in 2007. He then worked as a postdoctoral research scientist at Columbia University Medical Center in New York City (USA) for 4 years where he got mainly trained in basic cardiology. He was granted a European Marie-Curie Fellowship (2011) and a European Society of Cardiology grant (2012) to build up a team on human pluripotent stem cell-derived cardiomyocytes at Masaryk University Faculty of Medicine in Brno (Czech Republic). Albano was recruited as a permanent researcher by the French National Institute for Health and Medical Research (INSERM) in 2014. He has experience in basic cardiac physiology, calcium handling, ion channel biophysics, as well as in human pluripotent stem cell-derived cardiomyocytes to model inherited cardiac arrhythmias. He is also a nucleus member of the Scientists of Tomorrow of the European Society of Cardiology.