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Squish and squeeze – Nuclear mechanics and mechanotransduction in physiology and disease

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ABSTRACT:

The nucleus is the characteristic feature of eukaryotic cells and houses the genomic information of the cell. The nucleus and the nuclear envelope, which separates the nucleus from the cytoplasm, have traditionally been viewed primarily from a biochemical perspective in providing a distinct intracellular compartment for DNA transcription and replication. Only recently have the biophysical and biomechanical properties of the nucleus emerged as crucial regulators of cellular function. My laboratory is combining cell and molecular biology approaches with microfabricated devices that mimic physiological environments, live-cell microscopy, and in vivo models to investigate how physical forces acting on the nucleus, for example, in contracting muscle cells or during migration of cells through tight interstitial spaces, can challenge the integrity of the nucleus, alter its structure, and cause genomic and transcriptional changes. These processes play important roles in cellular mechanotransduction, i.e., the ability of cells to convert mechanical stimuli into biochemical signals, but can also contribute to various diseases when the nuclear structure is perturbed by mutations or altered protein expression. In particular, mutations in the nuclear envelope proteins lamin A/C are responsible for a broad spectrum of diseases (laminopathies), including Emery-Dreifuss muscular dystrophy (EDMD) and dilated cardiomyopathy. Despite extensive research efforts over the past two decades, the molecular mechanisms underlying these diseases remain incompletely understood. The fact that most mutations result in highly tissue-specific disease phenotypes primarily affecting skeletal and cardiac muscles, in spite of the near ubiquitous expression of lamins A/C, suggest that lamin mutations may render cells more sensitive to mechanical stress, which then causes progressive cell failure in mechanically stressed tissues. We have previously demonstrated that lamin A/C mutations that cause muscular dystrophy and dilated cardiomyopathy often result in impaired nuclear stability, disrupted nucleo-cytoskeletal coupling, and impaired activation of mechanosensitive genes. I will discuss new findings in this research area that highlight the importance of lamins A/C in mediating nuclear stability and mechanotransduction in mechanically stressed cells and tissues. At the same time, increased nuclear deformability, caused for example by reduced levels of lamins A/C, can promote cell migration through tight spaces with cross-sections smaller than the nuclear diameter, where the large size and rigidity of the nucleus can constitute a rate-limiting factor. I will present recent findings that demonstrate the importance of nuclear mechanics during cell migration in confined environments in vitro and in vivo, as well as the functional consequences of cells having to squeeze their large nuclei through tight interstitial spaces and small pores in the extracellular matrix network. Our studies indicate that the intracellular stresses acting on the cell nucleus during confined migration can result in transient nuclear envelope rupture and DNA damage, which is highly relevant to cancer cell migration but could also impact the function of immune cells. Our recent findings reveal specific differences in nuclear deformability and nuclear envelope composition in particularly aggressive breast cancer cells, as well as new insights governing the biophysical mechanisms by which cells are able to squeeze their large nucleus through tight spaces.