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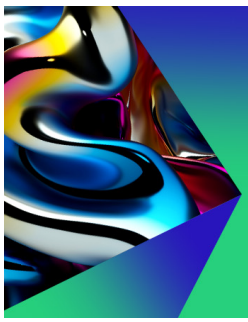

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INTRODUCTION

For nearly two decades, cellular responses to their environment—whether from chemical, molecular, or physical stimuli—have been well appreciated. These responses range from cell proliferation to differentiation, hypertrophy, migration, and even apoptosis.[1–3] However, despite years of investigation, we are still learning how mechanical forces are first transmitted across the cell to sites of mechanotransduction, where they are transformed into biochemical signals, then propagated by signaling pathways, and finally translated into specific molecular processes that enable the cell to respond and adapt to the mechanical input. In particular, while it has long been hypothesized that extracellular forces transmitted to the nucleus via the cytoskeleton have the potential to alter the arrangement and conformation of chromatin in the nucleus and thereby change gene expression,[4] only recently have we begun to understand the underlying mechanisms by which this may be accomplished.[5,6] Indeed, nuclear mechanotransduction has recently emerged as one of the primary mechanisms by which cells sense their local microenvironment and respond via transcriptional changes,[7] epigenetic regulation,[8,9] alternative splicing,[10] as well as signaling mechanisms independent of transcription, such as phosphorylation of inner nuclear membrane proteins[11] or recruitment of signaling enzymes to the inner nuclear membranes, where they can initiate inflammatory[12] and cell contractility pathways.[13,14]

In addition to participating in cellular mechanotransduction, it has further emerged that the physical properties of the nucleus, which is the largest and most rigid cellular organelle, are critical for cellular functions, including migration through confining 3D environments and resisting mechanical stress in muscle tissue.[15] Changes in the mechanical stability and deformability of the nucleus due to mutations in genes encoding nuclear envelope proteins, such as lamins, or changes in their expression can consequently result in muscular dystrophy and heart disease and promote cancer metastasis.[16–18] Due to the complexity and biological significance of nuclear mechanobiology, the number of publications on this topic has rapidly accelerated, resulting in new insights of fundamental mechanisms of nuclear mechanics and mechanotransduction, along with their often disease-related consequences. In this special collection in *APL Bioengineering*, leading experts in the field have surveyed current scientific issues and discuss our current understanding of the mechanobiology of the nucleus, thereby providing a timely overview of these topics, ranging from methods to applications.

METHODS TO MEASURE NUCLEAR MECHANICS

To understand nuclear structure-function relationships, one must first appreciate the experimental methods used to alter and probe nuclear mechanics. This collection contains several helpful surveys of methods to probe the mechanical properties of the nucleus and its detailed structure. Hobson *et al.* comprehensively discuss methods to measure nuclear mechanics and elicit nuclear responses by applying forces via cantilevers, tweezers, waves, and compression and stretch devices. Importantly, these methods span a range of length and time scales; thus, it is important to appreciate which method is appropriate for what question, and the review provides practical guidance to the reader.[19] For example, if one wants to determine if the nuclear lamina strain stiffens, large extensions via micropipette assays may be preferable.[20] The review by Lorber and Volk points to another important consideration, namely, the analysis of nuclear structure in fixed vs live cells. Discussing recent work in which the mesoscale chromatin organization was visualized in living organisms, they note that in

Drosophila muscle nuclei, chromatin is restricted to the nuclear periphery instead of filling the entire nuclear volume, with both transcriptionally active and silent chromatin distributed at the nuclear periphery, unlike what had been observed in fixed cells.[21]

MECHANOBIOLOGY OF NUCLEAR STRUCTURES

A robust understanding of nuclear mechanotransduction further requires an appreciation of nuclear structures and their role in transmitting and transducing forces as well as the tools needed to alter and probe nuclear mechanics. This collection principally focuses on force transduction via the nuclear envelope, including nuclear pores and lamins, and chromatin, especially its organization and response to mechanical forces. Tissue-level or cell-generated mechanical forces are transmitted to chromatin via the cell membrane, cytoskeleton, and nuclear envelope (Fig. 1).[6,22] At the nuclear envelope, membrane tension can modulate transport across nuclear pores (reviewed in Ref. 23), and forces are transmitted to the nuclear interior via the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex. Dickinson *et al.* note that although the nucleus is generally described as relatively stiff and viscous,[24] nuclear shape is quite dynamic and can be easily affected by the forces from the cytoskeleton during migration or cell spreading, as long as these shape changes do not require increases in nuclear surface area.[25] One consequence of large nuclear deformation is an increase in nuclear membrane tension. Shen *et al.* discuss the mechanism by which increased nuclear membrane tension, along with stretch-mediated calcium influx, results in the recruitment of cytosolic phospholipase A2 (cPLA2) and other proteins to the nuclear membranes, where cPLA2 can activate lipid hormone pathways such as the eicosanoid cascade and other signaling pathways, thus providing a novel nuclear mechanotransduction mechanism.[26] Their review of nuclear membrane tension mediated mechanosensing also touches upon the newly emerging role of the nuclear pores in nuclear mechanotransduction. To regulate transport of larger

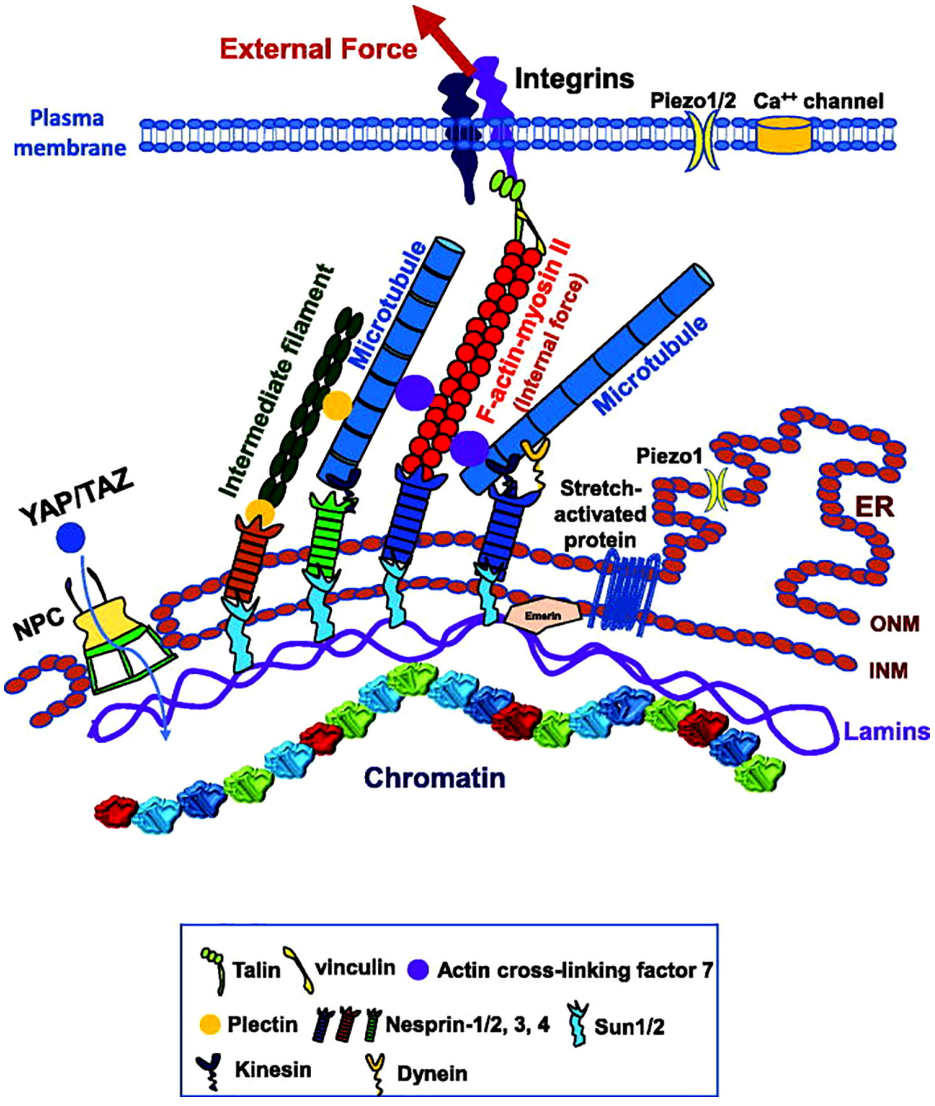

FIG. 1. The force transmission pathway from the cell surface to the chromatin. External forces are transmitted from the extracellular matrix proteins to the integrins, intracellular focal adhesion proteins (talin and vinculin and other proteins), filamentous actin (F-actin) (which is associated with non-muscle myosin II), and from F-actin to the LINC (linker of nucleoskeleton and cytoskeleton) complex (nesprins and Sun1/2), to the nuclear lamina networks, and then to the chromatin. ONM, outer nuclear membrane; INM, inner nuclear membrane; ER, endoplasmic reticulum. Plasma membrane deformation by the large force can also open Piezo1/2 mechanosensitive channels and stretch-activated calcium channels to signal or causes YAP/TAZ to translocate into the nucleus via the nuclear pores. Piezo1 on the endoplasmic reticulum can be activated to release intracellular calcium. Stretch-activated protein, a putative protein at the nuclear membranes which responds to mechanical stretch. For brevity, the force pathway via cell–cell adhesion molecules is not drawn. Reproduced with permission from Amar *et al.*, APL Bioeng. **5**, 041503 (2021). Copyright 2021 Authors, licensed under a Creative Commons Attribution (CC BY) license.

proteins across the nuclear envelope, thousands of nuclear pores dot the nuclear surface and control the bidirectional transport of proteins larger than ∼30–60 kDa in size. Traditionally, nucleo-cytoplasmic transport has been considered to be exclusively driven by specific nuclear import and export signals, but in their review, Matsuda and Mofrad discuss recent findings that indicate that the NPC is itself mechanically sensitive, changing its channel diameter depending on nuclear membrane tension to modulate nucleo-cytoplasmic transport,[27] in much the same manner in which mechano-sensitive ion channels in the plasma membrane and endoplasmic reticulum function.[28]

Forces are transmitted to the nuclear interior via the nuclear lamina and applied to heterochromatin.[6,22] Lamins are type V intermediate filament proteins that are extremely ductile and highly distensible,[29] and these attributes can change with cell differentiation and disease.[30] The nuclear envelope also must transmit "outside-in" forces and, consequently, dictate nuclear shape. To accomplish this, transmembrane linker complexes, e.g., nesprins and SUN proteins, which form the LINC complex, connect the cytoskeleton to nuclear lamins.[29] On the other hand, lamins attach to gene-poor, transcriptionally repressed heterochromatin regions, also known as lamina associated domains (LADs). As forces are transmitted to the nucleus, they may result in chromatin deformation and opening, promoting transcription of mechanoresponsive genes. Wang *et al.* note that this process is highly tissue-specific and lamin-specific; expression of different lamin genes associate with mechanosensitive factors vs cell cycle regulation.[18] Through a separate mechanism, contributions from each of these structures to the nucleus may allow chromatin to phase separate and form domains, which have significant functional implications for cell physiology and are reviewed in Lee *et al.*[31]

APPLICATIONS TO NUCLEAR MECHANOBIOLOGY

Nuclear mechanobiology plays key roles in regulating cell responses[1–3] in many cell types. For example, Jain *et al.* focused on macrophages, noting key changes in their activation and dynamic signaling that result from the exposure of cells to micropatterned surfaces, stiff substrates, and high forces.[32] These findings raise the intriguing possibility that physical cues from the microenvironment, in addition to the established chemical cues, can modulate specific immune responses. Nucleus-based mechanisms were critical in these responses, e.g., nuclear translocation of transcription factors, epigenetic modifications, and even DNA methylation. Insights such as these will continue to deepen our understanding of how the nucleus regulates cell behavior, and, in turn, how the physical world around the nucleus shapes it. Yet, many gaps remain in our understanding of mechanobiology's implications, not just in macrophages, but in all aspects of life, begging further study of these structures, methods, and applications. For example while forces are transmitted to the nucleus,[33] the following remain to be elucidated: (i) how those forces are transmitted to the nucleus, (ii) how they alter chromatin organization, (iii) how they increase expression of specific genes, and (iv) how nuclear mechanotransduction—including through the nuclear membranes, nuclear pores, and chromatin—is coordinated with cytoplasmic mechanotransduction processes. While many other systems beyond macrophages are known to be influenced by nuclear mechanotransduction, e.g., muscular dystrophy[16] and dilated cardiomyopathy,[34] our understanding of how forces impact gene expression remains limited. Additional insights are required to understand how altered nuclear mechanotransduction and/or increased nuclear fragility contribute to tissue specific phenotypes and to develop effective treatment approaches for these devastating diseases, providing further motivation for continued advances in nuclear mechanobiology.

CONCLUSIONS

The mechanobiology of the nucleus has emerged as a rapidly growing research area driven by exciting discoveries on the role of nuclear mechanics and mechanotransduction in numerous physiological and pathological processes. Much of this growth has been fueled by newly developed experimental methods and clever combination of precise mechanical manipulation and molecular biology techniques to record cellular responses. The application of nuclear mechanobiology to new research areas, particularly when combined with ongoing advances in microscopy and genomics-based techniques, is expected to lead to even deeper insights how the interplay between the nucleus and the physical forces acting on it play a central role in cellular function and decision making.

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