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Review

Cellular mechanosensing: Getting to the nucleus of it all

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ABSTRACT

Cells respond to mechanical forces by activating specific genes and signaling pathways that allow the cells to adapt to their physical environment. Examples include muscle growth in response to exercise, bone remodeling based on their mechanical load, or endothelial cells aligning under fluid shear stress. While the involved downstream signaling pathways and mechanoresponsive genes are generally well characterized, many of the molecular mechanisms of the initiating 'mechanosensing' remain still elusive. In this review, we discuss recent findings and accumulating evidence suggesting that the cell nucleus plays a crucial role in cellular mechanotransduction, including processing incoming mechanoresponsive signals and even directly responding to mechanical forces. Consequently, mutations in the involved proteins or changes in nuclear envelope composition can directly impact mechanotransduction signaling and contribute to the development and progression of a variety of human diseases, including muscular dystrophy, cancer, and the focus of this review, dilated cardiomyopathy. Improved insights into the molecular mechanisms underlying nuclear mechanotransduction, brought in part by the emergence of new technologies to study intracellular mechanics at high spatial and temporal resolution, will not only result in a better understanding of cellular mechanosensing in normal cells but may also lead to the development of novel therapies in the many diseases linked to defects in nuclear envelope proteins.

Contents

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1. Introduction

Mechanotransduction describes the cellular and molecular processes of converting mechanical stimuli into biochemical signals. Since the discovery of stretch sensitive ion channels, the field has rapidly expanded, leading to the discovery of various force sensitive proteins within the cytoplasm and plasma membrane, such as titin, talin, vinculin, and p130Cas (Seifert and Grater, 2013). Disturbed cellular mechanotransduction causes numerous defects on the cell, tissue, and organ level (Jaalouk and Lammerding, 2009); thus, it only seems logical that the human heart, which beats on average 2.5 billion times over the course of a lifetime, requires tightly regulated and robust mechanoregulation. Beyond this, the importance of mechanoelectric feedback adds another layer of complexity to cardiac mechanotransduction. For instance, ion channels such as Cav1.2 and the TRP family of ion channels have specific locations in the heart and enable organ level responses to pressure and volume fluctuations by helping regulate action potentials (Takahashi et al., 2013). Connexins, transmembrane proteins important for gap junction formation, may act as effectors to coordinate excitation-contraction coupling (Meens et al., 2013). Beyond this, connexin-43 is upregulated in response to mechanical stimulation and precedes other cell–cell junction formations. While mechanosensing at the plasma membrane and the cytoskeleton has been well studied, our knowledge quickly diminishes as we probe deeper into (cardiac) cells. It is clear that cardiac myocyte nuclei undergo substantial deformations during contraction (Fig. 1); however, one remaining central question in cardiac mechanobiology and mechanobiology in general, revolves around the extent to which the nucleus itself can act as a mechanosensor.

A mechanosensor, as we will define it, is a protein (or, more generally, a cellular structure) that translates a mechanical input into a biochemical output, thereby initiating mechanoresponsive signaling pathways. Typically, molecular mechanosensing involves force induced conformational changes, resulting in altered interaction with binding partners or modulation of (protein) activity. It is well established that the nucleus plays an important role in mechanotransduction signaling, i.e., the process of biochemical signal propagation and processing, as most signaling pathways eventually culminate with nuclear proteins binding to specific genomic elements to modulate transcription. It is also known that the nucleus is mechanically connected to the rest of the cell via LINC (**Li**nker of **N**ucleoskeleton and **C**ytoskeleton) complex structures in the nuclear envelope. These complexes are akin to focal adhesions at the plasma membrane, allowing for cytoskeletal and external forces to result in nuclear deformations (Lombardi and Lammerding, 2011). But, the question remains: can mechanically induced nuclear deformations directly control gene expression in a predictable, biologically-meaningful way? If so, what are the molecular mechanisms that enable the nucleus to sense and respond in this way? What are the implications for cardiac function in health and disease? Are there cardiac specific mechanisms for nuclear mechanotransduction?

The emergence of new technologies—ranging from advanced imaging and bioengineering approaches for cell-based assays, to molecular probes that can detect nanoscale forces and deformations—has enabled the scientific community to finally start addressing this important question. In the following sections, we will briefly outline current models of nuclear mechanotransduction before discussing how recent findings, ranging from cellular and subcellular studies to human diseases, and corresponding disease models are beginning to shape a clearer portrait of the nucleus as both a mechanosensor and a central processing hub for mechanoresponsive signaling pathways. Lastly, we will highlight how recent and ongoing advances in technology development will help to further elucidate the fascinating biology of nuclear mechanotransduction and its role in human health and disease.

2. The nucleus at the center of the cell

A basic overview of the mechanical connectivity linking the nucleus to the rest of the cell and its ECM surroundings (Fig. 2) provides a helpful roadmap for understanding how the nucleus may carry out mechanotransduction processes. The nucleus is encapsulated by a double lipid membrane system, composed of the

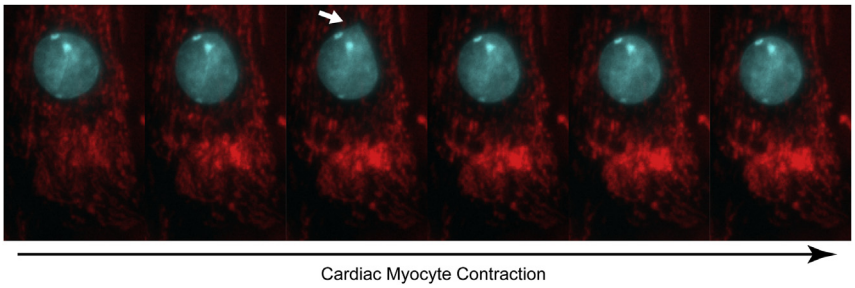

Fig. 1. Nuclear deformation during cardiac myocyte contraction. Time-lapse sequence of a mouse neonatal cardiac myocyte spontaneously contracting in culture; the cytoskeleton exerts substantial forces on the cell nucleus (blue), resulting in reversible large nuclear deformations (white arrow). Mitochondria are shown in red.