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Probing compressibility of the nuclear interior in wild-type and lamin deficient cells using microscopic imaging and computational modeling

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ABSTRACT

Mechanical properties of the cell nucleus play an important role in maintaining the integrity of the genome and controlling the cellular force balance. Irregularities in these properties have been related to disruption of a variety of force-dependent processes in the cell, such as migration, division, growth or differentiation. Characterizing mechanical properties of the cell nucleus *in situ* and relating these parameters to cellular phenotypes remain challenging tasks, as conventional micromanipulation techniques do not allow direct probing of intracellular structures. Here, we present a framework based on light microscopic imaging and automated mechanical modeling that enables characterization of the compressibility of the nuclear interior *in situ*. Based entirely on optical methods, our approach does not require application of destructive or contacting techniques and it enables measurements of a significantly larger number of cells. Compressibility, in this paper represented by Poisson's ratio ν, is determined by fitting a numerical model to experimentally observed time series of microscopic images of fluorescent cell nuclei in which bleached patterns are introduced. In a proof-of-principle study, this framework was applied to estimate ν in wild type cells and cells lacking important structural proteins of the nuclear envelope ($LMNA^{-/-}$). Based on measurements of a large number of cells, our study revealed distinctive changes in compressibility of the nuclear interior between these two cell types. Our method allows an automated, contact-free estimation of mechanical properties of intracellular structures. Combined with knockdown and overexpression screens, it paves the way towards a high-throughput measurement of intracellular mechanical properties in functional phenotyping screens.

1. Introduction

The cell nucleus provides eukaryotic cells with a functional scaffold to store and protect the genome while at the same time ensuring the proper execution of essential process (Iborra and Cook, 2002). The mechanical properties of the cell nucleus maintain the integrity of the genome and contribute to the cellular force balance (Rowat et al., 2008; Dahl et al., 2010). Irregularities in these properties are related to alterations of force-dependent processes like migration, division, growth and differentiation and thus play an important role in the development of diseases like the laminopathies (Broers et al., 2004) and cancer (Kumar and Weaver, 2009).

A variety of biophysical assays coupled with *in silico* analyses have been developed to determine the mechanical properties of cells for diverse purposes and at different spatial scales (Vaziri and Gopinath, 2007). Most of these methods are based on calculation of the cellular response to application of external loads onto the cellular membrane. The extension of these techniques devoted to the study of whole cell mechanics to the biomechanical analysis of intracellular structures such as cell nuclei is not straightforward, since these structures are not accessible for direct mechanical contact in a non-destructive way. Many existing approaches to investigate nuclear mechanics rely on prior isolation of cell nuclei (Lammerding et al., 2007; Vaziri et al., 2006; Vaziri and Mofrad, 2007; Guilak et al., 2000), removing them from the physiological environment inside the cell, i.e. the physiological concentrations of salts, which has been shown to alter nuclear mechanical properties (Dahl et al., 2005). Other experimental setups require time-expensive and extensive procedures that complicate the reproducibility of experiments and limit the throughput. Recently developed optical stretchers (Guck et al., 2001, 2005) enable a contactless probing of thousands of cells. However, these methods are incapable of extracting the contribution of the nucleus on the overall cellular response, and thus cannot be applied to measure the material properties of the cell nucleus. An automated analysis of nuclear mechanics is of particular interest for medical research,

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