High-throughput mechanical cellular phenotyping by combined optical stretching and computational modeling

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Mechanical properties of the cell nucleus play an important role in maintaining the integrity of the genome and controlling the cellular force balance. The structural integrity of the nuclear interior is required for the simultaneous performance of essential biochemical processes such as replication, transcription and splicing. The nuclear functional architecture depends on the material properties of the cell nucleus. Irregularities in these properties have been related to a variety of force-dependent processes in the cell, such as migration, division, growth or differentiation. Characterizing the mechanical properties of the cell nucleus in situ and relating these parameters to cellular phenotypes or disease states remains a challenging task. Previous approaches of experimental cell mechanics are based on micromanipulation techniques that employ application of controlled forces onto the cellular boundary. Consequently, these methods provide information about the overall cell properties (e.g., stiffness of the entire cell) or those of its part that are directly accessible by the measurement (e.g., cell membrane). Probing mechanical properties of intra-cellular structures that are not accessible for direct measurement is not possible with conventional micromanipulation techniques. Furthermore, most conventional methods require time-consuming “one man – one cell” procedures restricting these approaches to very small numbers of experiments. Here, we present a general framework for large-scale functional mechanical cellular phenotyping that allows the determination of material properties for thousands of cells on a single cell basis. This approach combines contactless optical stretching of cells and model based analysis of time-series of microscopic images of these optically stretched cells. In a proof-of-concept study this framework was applied to estimate mechanical properties of various cell types under functional perturbations by RNAi and chemical drugs known to interfere with the cellular integrity. Combination of model-based image analysis with optical cell stretching paves the way for high-throughput molecular and mechanical cellular phenotyping with manifold applications in quantitative biology and molecular medicine.