MECHANISM OF THE SPATIAL COORDINATION BETWEEN CELL AND NUCLEAR SHAPE

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ABSTRACT

Changes in cell morphology play a crucial role in the microarchitecture of many human tis- sues and are commonly associated with alterations of nuclear shape. However, there is still no mechanistic understanding of the internal orchestration between cell and nuclear shape. In this paper, we shape-engineered single endothelial cells to quantitatively and non-invasively assess the nuclear morphology and the intracellular force balance in response to cell shape changes. Our study reveals for the first time that nuclear orientation and deformation are regulated by lateral compressive forces driven by increased tension in actomyosin filaments. We propose a simple mechanical model that quantitatively accounts for our experimental data and provides a conceptual framework for the spatial coordination between cell and nuclear shape.

KEY WORDS: Endothelial cells, nucleus, cytoskeleton, intracellular forces, actomyosin filaments

INTRODUCTION

One of the most fundamental problems in tissue morphogenesis is the question of how changes in cell shape produce alterations of nuclear form and functions [1,2]. Indeed, large-scale changes in cell morphology require coordinated temporal and spatial regulations of cellular subdomains and in turn are commonly associated with nuclear shape remodeling in endothelial cells [3] and other cell types [4]. Nuclear deformations in response to cell shape changes have been suggested to affect both protein synthesis and gene expression [5] and one proposed mechanism for the transduction of cell shape information into gene expression is through mechanical forces trans- mitted by means of the direct link of the cytoskeleton with the nucleus [6].

Although significant advances have been made in terms of identifying the proteins involved in these bonds [7], little is known about the mechanism of force transfer from the cytoskeleton to the nucleus, related to the alteration of the internal cytoskeletal force balance by changes in cell shape. Interestingly, a recent study [8] suggests that the nucleus balances a portion of the actomyosin tension in the cell, which is consistent with the recent discovery [9] of a contractile actin structure wrapped around the nucleus and suggested to be involved in the nuclear shape control.

However, how mechanically intracellular forces exerted by actomyosin filaments, and asso- ciated with cell shape changes, act on the nucleus to directly impact upon the nuclear machinery are still poorly understood [10]. Therefore, a unifying mechanism that links together all of these fragmentary observations must exist to explain in details the cascade of mechanical events involving cell morphology, cytoskeletal organization, cell-substrate adhesion, intracellular force balance and nuclear shape and functions.

Our goals in this study were to define the steps and mechanisms underlying nuclear shape and structure remodeling during large-scale changes of endothelial cell shape, by determining how morphological modifications of cell shape produce alterations of the cellular mechanical force balance. By using micropatterned surfaces to control shape and spreading area of single endothelial cells, we show that deformation and orientation of the nucleus in response to cell shape changes are controlled by intracellular compressive forces. We demonstrate that these compressive forces are mainly driven laterally to the nucleus by increased tension in thick actomyosin fibers. We show that tension is gradually generated by anisotropic force contraction dipoles as the cell elongates. The contraction forces have a dramatic effect on the nucleus itself. Indeed, our findings indicate a loss of nuclear volume by 50% in deformed nuclei that results in a drastic chromatin condensation. To quantify these various effects, we have devised a simple physical model that relates the spatial organization of actin stress fibers to the lateral compressive forces imposed on the nucleus. This mechanical model is able to quantitatively describe the main features of nuclear shape remodeling and provides a conceptual framework for the mechanical regulation of nuclear shape and functions in response to large-scale changes in cell shape.

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