Hierarchical Structure Controls Nanomechanical Properties of Vimentin Intermediate Filaments

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HIERARCHICAL STRUCTURE CONTROLS NANOMECHANICAL PROPERTIES OF VIMENTIN INTERMEDIATE FILAMENTS

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INTRODUCTION

Intermediate filaments (often abbreviated as IFs), in addition to microtubules and microfilaments, are one of the three major components of the cytoskeleton in eukaryotic cells (Figure 1). It has been suggested that intermediate filaments are crucial in defining key mechanical functions of cells such as cell migration, cell division and mechanotransduction, and have also been referred to as the "safety belts of cells" reflecting their role in preventing exceedingly large cell stretch [1, 2]. Vimentin is a specific type of this protein filament found in fibroblasts, leukocytes, and blood vessel endothelial cells, representing the most widely distributed type of intermediate filaments. Several diseases have been linked to the structure and density of intermediate filaments. Here we report a systematic study of the effects of intermediate filaments on cell mechanics, specifically focused on changes in the density of filaments. We compare the results with experimental studies in vimentin deficient cells, showing good qualitative agreement.

RESULTS

By utilizing a simple empirical coarse-grained computational model of the intermediate filament network in eukaryotic cells (Figure 2), here we probe cell mechanical behavior at large deformation by mimicking an optical tweezers test.

Figure 3 shows snapshots of the cells as they undergo tensile deformation. Figure 4 plots the mechanical response of the cell under tension for several intermediate filament densities, comparing the computational predictions with experimental results reported earlier in [3]. Figure 4A,B show the strain-force and stiffness-force curves for cell models with high density (blue curve, with 40 intermediate filaments) and low density (pink curve, with 10 intermediate filaments, representing a 75% reduction in intermediate filament density) of intermediate filaments. Figure 4C,D show the angle of twist (=angular strain)-stress curves and stiffness-stress curves for adherent wild-type and intermediate filament-deficient fibroblasts. As the intermediate filament density decreases, the cell mechanical properties exhibit greater softening and a reduced stiffness. The results show that intermediate filament deficient cells display an altered mechanical behavior, featuring a softer mechanical response at large deformation while the mechanical properties remain largely unchanged under small deformation. The computational results are qualitatively consistent with the experimental measurements.

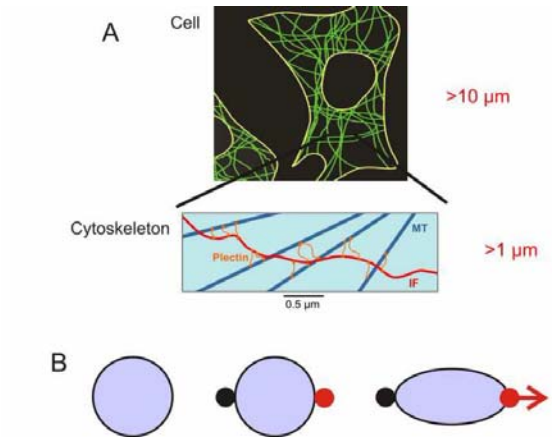

Figure 1. Simple schematic of the cell and the underlying cytoskeletal structure (panel A) and loading geometry used for the single cell stretching experiments (panel B).

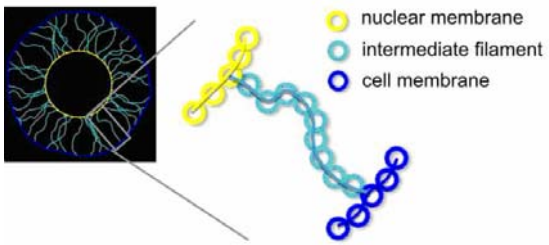

Figure 2: Schematic of the cell model (left) and the coarse-grained model (right), along with a description of the coarse-grained bead-spring model.

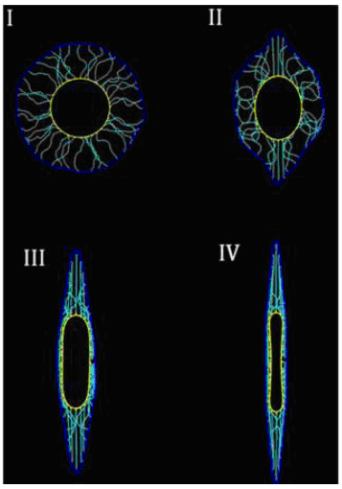

Figure 3: Snapshot of the cell as it undergoes tensile deformation as indicated in the schematic in Figure 1B.

Figure 5 shows snapshots of cell models with 40 intermediate filaments (snapshot I), 20 intermediate filaments (snapshot II) and 10 intermediate filaments (snapshot III) at an applied tensile strain of 48%. We observe that the nucleus is increasingly stretched as the intermediate filament density increases. The results show that at a given strain, the more intermediate filaments the cell contains, more stretched is the nucleus.

DISCUSSION

Our results suggest that intermediate filaments contribute to cell stiffness and deformation at large deformation, and thus play a significant role in maintaining cell structural integrity in response to applied stress and strain. Our model opens the door to future studies to investigate disease states, the effects of amino acid mutations, and how structural changes at different levels in the cell's structural makeup influence biomechanical properties.

Multi-scale models of cells may open the door to applications with significant payoff in medicine, biological engineering, materials science and material engineering. As pointed out in [4], the long-term impact of this work could be used to predict diseases in the context of diagnostic tools by measuring material properties rather than focusing on symptomatic chemical readings alone. The change of cell stiffness under various disease states (e.g. cancer, infectious disease, genetic diseases such as muscle dystrophies) may provide novel opportunities for characterization and treatment at early disease states. An extension of the model used here could be used to formulate a cell model by extending it to include other cytoskeletal elements and their dynamical interaction, or perhaps to extend the model to a fully three dimensional representation of the cell.

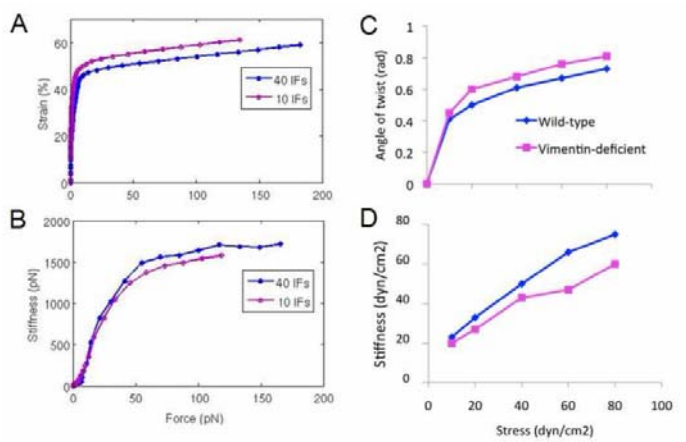

Figure 4: Mechanical response of the cell under tension for several intermediate filament densities, as predicted by the mesoscale model (panels A and B), as well as a qualitative comparison with experimental results (panels C and D, adapted from [3]).

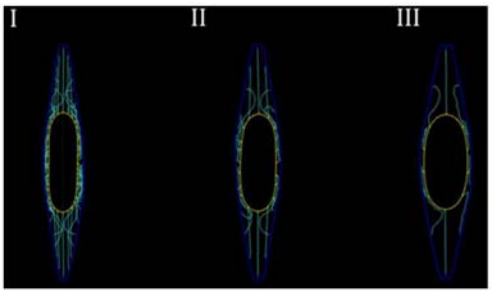

Figure 5: Snapshots of the cell model deformation under different intermediate filament densities. The plot shows snapshots of cell models with 40 intermediate filaments (snapshot I), 20 intermediate filaments (snapshot II) and 10 intermediate filaments (snapshot III) at a laterally applied tensile strain of 48%. We observe that the nucleus is increasingly stretched as the intermediate filament density increases. At a given strain, the more intermediate filaments, the stiffer the cell is, then the higher is the stress and thus the more stretched is the nucleus.

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