Mechanics before Chemistry: Tensile Stress Induced Cytoskeletal Reorganization

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***Short Abstract* — Cellular remodeling in response to mechanical stimuli is critical for understanding mechano-signal transduction. We hypothesize that external stress induced subcellular adaption is accomplished through dynamical cytoskeletal reorganization. To study the interactions between subcellular structures involved in transducing mechanical signals, we combined experimental and modeling approaches to measure real-time structural and mechanical adaption of the actin cytoskeletal network. In vitro, we imaged the actin cytoskeleton as tensile stress was applied to live vascular smooth muscle cells (VSMC) using an ECM-functionalized atomic force microscope probe. In silico, we modeled the mechanochemical coupling of the actin cytoskeleton network. Both experimental and modeling results agree that under tensile stress, mechanical structural adaptation occurs before chemical adaptation: actin filaments align first, then actin polymerization takes place to further restructure the cytoskeleton.**

***Keywords* — Cytoskeletal Network, Tensile Stress, Filament Alignment, Actin Polymerization**

I. Introduction

CELLS interact with a complex microenvironment. Among all the microenvironmental stimuli, mechanical stress [1, 2] is important in many biological and physiological processes. Vascular smooth muscle cells (VSMC) are subjected to the cyclic stretch of pulsatile blood pressure that deforms the extracellular matrix and induces axial and circumferential wall stresses [3]. However, how VSMC responds to the mechanism of axial stress in the vessel wall, which can be considered as tensile stress applied to cell, is not well-understood [4]. We combine experimental and modeling approaches to investigate the effects of tensile stress on the dynamic remodeling of the cytoskeleton network.

II. Methods

The tensile stress was applied to live VSMC using an atomic force microscope probe functionalized with extracellular matrix proteins. Mechanical stimulation of the cell at low (~0.5 nN) and high (~1 nN) magnitude forces was applied every 3–5 min for 20–25 min each and the actin cytoskeleton was imaged by spinning-disk confocal microscopy after each force application [3].

A computational model for mechanochemical dynamics of active network (MEDYAN) [5] was used to simulate the actin network with an external pulling force. The model considers actin fibers as semi-flexible polymers embedded in a solution of actin monomers, alpha-actinin cross-linking proteins, and non-muscle myosin II (NMII) motors. A system of reaction-diffusion equations describes the spatiotemporal dynamics of actin polymerization and actomyosin network formation. In a simulation volume of $1\times1\times1$ μm^3, a randomly initialized actin filament network was subjected to an external pulling force. We varied the strength of force, and measured the resulting fiber alignment, polymerization, and uniformity.

III. Results

Both experimental and simulation results show that tensile stress has significant effect on the dynamics of the cytoskeleton network: as the tensile stress increases, the fibers rearrange to increase alignment along the direction of the external stress, before fiber polymerization takes place. This result suggests mechanical structural adaptation operates at a shorter timescale than biochemical processes, which can have important implications to mechano-signal transduction.

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