Integrative Model of Actin, Adhesion, and Signaling Dynamics at the Leading Edge of Migrating Cells

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***Short Abstract* — We have constructed a spatiotemporal model that incorporates adhesion, cytoskeletal and signaling dynamics governing protrusion of lamellipodia in mesenchymal cells. The model includes actin polymerization at the leading edge and the resulting retrograde flow of the F-actin network. Nascent adhesions promote actin polymerization via Rac signaling and interact with the F-actin network to activate RhoA. Consequently, myosin II is activated and applies contractile stress on the F-actin network. Our model predicts an optimal adhesion density for maximal protrusion velocity. Moreover, myosin contractility is limited in its ability to control protrusion velocity, unless global tension of the membrane boundary is considered.**

I. Extended Abstract

Cell migration plays a crucial role in a wide variety of biological processes. It is essential in wound healing, embryonic development, cancer metastasis as well as innate and adaptive immunity. Amongst the different cell migration phenotypes, amoeboid and mesenchymal motility modes lie at opposite extremes. The mesenchymal migration phenotype is characterized by slow locomotion, strong adhesions mostly with extracellular matrix (ECM), and a distinct actin cytoskeletal and myosin spatial profile [1]. In mesenchymal and epithelial cells, integrins orchestrate the dynamics of the actin cytoskeleton, responsible for force generation, adhesion complexes, responsible for force transduction, and biochemical regulatory networks, responsible for signal transduction [2]. Nascent adhesions form at the leading edge of migrating cells, where transmembrane integrins form attachments to ECM and to actin filaments during membrane protrusion in a myosin II-independent manner [3]. Nascent adhesions play an important signaling role in migrating cells. They activate Rac and other signaling pathways that further promote barbed end polymerization and protrusion, forming a positive feedback loop [4]. Moreover, adhesions under tension promote the activation of RhoA/ROCK signaling, which in turn activates myosin II [5]. Nascent adhesions also play a crucial role in force transduction. They bind with F-actin and create a mechanical clutch, allowing polymerizing actin to overcome membrane stress push the membrane forward [6].

Specific aspects of this system have been explored in previous models [7–10]. In this study, however, we have constructed a model that integrates and spatially resolves adhesion, cytoskeletal, and signaling dynamics in the lamellipodia of mesenchymal cells. We have modeled actin polymerization at the leading edge and the resulting retrograde flow of the F-actin network. Nascent adhesions promote actin polymerization via Rac signaling as well as interact with the F-actin network to activate RhoA. Subsequently, active myosin II engages and applies stress to the F-actin network. Our model predicts an optimal ECM (adhesion) density for maximal protrusion velocity. At lower ECM densities, not enough adhesions are formed, and most of the actin polymerization results in retrograde flow. At higher ECM densities, competition among increased barbed end density for G-actin and increased myosin activity reduce protrusion below optimum levels. Moreover, at low ECM densities, increasing total G-actin has limited effect on protrusion velocity as compared to increasing total G-actin at higher ECM densities. Lastly our model predicts that myosin is limited in its ability to limit protrusion, unless global tension of the membrane boundary is considered.

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