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A kinematic model coupling stress fiber dynamics with JNK activation in response to matrix stretching

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ABSTRACT

The role of the actin cytoskeleton in regulating mechanotransduction in response to external forces is complex and incompletely understood. Here, we develop a mathematical model coupling the dynamic disassembly and reassembly of actin stress fibers and associated focal adhesions to the activation of c-jun N-terminal kinase (JNK) in cells attached to deformable matrices. The model is based on the assumptions that stress fibers are pre-extended to a preferred level under static conditions and that perturbations from this preferred level destabilize the stress fibers. The subsequent reassembly of fibers upregulates the rate of JNK activation as a result of the formation of new integrin bonds within the associated focal adhesions. Numerical solutions of the model equations predict that different patterns of matrix stretch result in distinct temporal patterns in JNK activation that compare well with published experimental results. In the case of cyclic uniaxial stretching, stretch-induced JNK activation slowly subsides as stress fibers gradually reorient perpendicular to the stretch direction. In contrast, JNK activation is chronically elevated in response to cyclic equibiaxial stretch. A step change in either uniaxial or equibiaxial stretch results in a short, transient upregulation in JNK that quickly returns to the basal level as overly stretched stress fibers disassemble and are replaced by fibers assembled at the preferred level of stretch. In summary, the model describes a mechanism by which the dynamic properties of the actin cytoskeleton allow cells to adapt to applied forces through turnover and reorganization to modulate intracellular signaling.

1. Introduction

Adherent cells in many tissues, including arteries, bladder, muscle, and tendon, to name a few, are subjected to stretch as the tissue deforms in response to external forces. Mechanical stretch regulates many cell functions, including proliferation, apoptosis, migration and morphology that occur in response to stretch-induced changes in intracellular signaling and gene expression (Haga et al., 2007; Wang and Thampatty, 2006). While the mechanisms that regulate mechanotransduction remain unclear, focal adhesions and the actin cytoskeleton clearly plays a role (Bershadsky et al., 2003). It is well established that focal adhesions and stress fibers are interdependent. This is supported by the fact that focal adhesions anchor stress fibers to the matrix and the integrity of the actin cytoskeleton is necessary to maintain focal adhesions (Burridge and Fath, 1989; Volberg et al., 1994). Integrins have been implicated as mechanosensors responsible for stretch-induced intracellular signaling (Maniotis et al., 1997; Thodeti et al., 2009). Katsumi et al. (2005) reported that JNK activation in response to stretch requires the formation of new integrin–matrix bonds. We and others have shown that cells, along with their stress fibers and focal adhesions, orient perpendicular to the direction of cyclic uniaxial stretch (Kaunas et al., 2005; Wang et al., 2001; Yano et al., 1997). The time course of cyclic stretch-induced JNK activation corresponds with that of stress fiber realignment (Kaunas et al., 2006). Specifically, cyclic uniaxial stretch causes the transient activation of JNK that subsides as the stress fibers become oriented perpendicular to the direction of stretch. Stretch-induced stress fiber alignment occurs via disassembly and reassembly of stress fibers (Hayakawa et al., 2001), which would result in the formation of new integrin–matrix bonds at the associated focal adhesions. Together, these studies suggest that stretch-induced JNK activation is upregulated during times when stress fibers and their associated integrin–matrix adhesions are undergoing relatively high rates of disassembly and reassembly.

Integrin bond integrity has a complex dependence on the applied mechanical force. Integrins are activated by mechanical strain to increase binding affinity (Katsumi et al., 2005), indicating that force increases integrin binding. Further, focal adhesions

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form and grow in the direction of tension, as observed in response to micropipette pulling of the cell membrane (Riveline et al., 2001) or by actin–myosin contractility (Balaban et al., 2001). Conversely, inhibition of actin–myosin contractility decreases integrin clustering (Kawakami et al., 2001). Mechanical energy added to focal adhesions by pulling tends to increase the dissociation of focal adhesion proteins (Evans and Calderwood, 2007), indicating that excessive tension increases the likelihood of adhesion bond rupture. Lu et al. (2008) reported that large stretches (25%) rupture stress fibers, which would be expected to greatly reduce the tension on the associated focal adhesion, leading to their disassembly. Precise measurements of forces generated at cell attachments indicate that cells tend to maintain a constant level of stress applied to focal adhesions (Balaban et al., 2001). Together, these studies support the hypothesis that perturbing the stretch and/or tension in stress fibers and their associated focal adhesions either above or below an optimum level tends to destabilize these structures.

Recently, computational modeling has been used to elucidate the complex interplay between matrix deformation, cytoskeletal and integrin bond dynamics and stress fiber reorganization. Kong et al. (2008) proposed a model which predicts that, at steady state, stress fibers will orient in directions that avoid cyclic matrix stretch since excessive force causes the rupture of integrin–matrix bonds. De et al. (2007) proposed a model characterizing cells as force dipoles that are driven to align in order to regulate either the local stress or strain in the surrounding matrix. We provide the first computational analysis of stretch-induced mechanotransduction. To link the kinetics of intracellular signaling with the pattern of stretch, a model is needed that describes the temporal and spatial evolution of stress fiber organization in response to stretch. We have recently formulated a computational model of stress fiber dynamic reorganization based on constrained mixture theory (Humphrey, 2008) that successfully describes published time courses of stress fiber reorientation in response to cyclic uniaxial and equibiaxial stretches (Kaunas and Hsu, 2009). Based on the interdependence of stress fibers, integrins, and c-jun N-terminal kinase (JNK) activation, we coupled the stress fiber dynamics model to a kinetic model of JNK activation. By providing a quantitative framework, the results of our simulations provide valuable insight into the complex relationships between matrix stretch pattern, stress fiber dynamics, integrin turnover, and JNK signaling.

2. Methods

2.1. Overall strategy for modeling stretch-induced JNK activation

The model consists of two algorithms run consecutively. The first algorithm calculates stretch-induced stress fiber turnover and reorganization in response to a prescribed spatiotemporal pattern of matrix stretch. The results of the first algorithm are then used as the input to the second algorithm to compute the time course of stretch-induced JNK activation. The simulations are run in MATLAB (the MathWorks, Natick, MA) and the code is contained in the Supplemental Materials.

2.2. Kinematic model of stretch-induced stress fiber dynamics

A kinematic model of stretch-induced stress fiber reorganization was used to simulate the gradual turnover and reorientation of stress fibers in response to stretching of the matrix upon which the cells are attached (Kaunas and Hsu, 2009). Here we only briefly describe the model of stress fiber reorganization. The details of the model can be found in the Supplemental Materials. Cells are assumed to contain a population of load-bearing stress fibers that are constrained to move together as the matrix deforms. The stress fibers are grouped into individual families of fibers where the fibers in family i share the same orientation and level of stretch. Motivated by the observations that fiber disassembly is upregulated by either releasing or increasing the fiber prestretch (Lu et al., 2008), the rate of disassembly of fibers from family i is described by a differential equation,

$$\frac{d\varphi^i(t)}{dt} = -k_0\left[1 + k_1\left(\frac{\alpha^i - \alpha_0}{\alpha_0}\right)^2\right]\varphi^i(t) \tag{1}$$

where φ^i is the mass fraction of fiber family i, and α^i is its stretch ratio defined as the ratio of the current length of the stress fiber and the length when there is no tension in the stress fiber. Thus, the rate of disassembly of fiber family i is proportional to the normalized deviation between the fiber stretch and an equilibrium level of stretch α_0. Stress fibers are assumed to reassemble immediately with the assembled fiber mass distributed uniformly in all directions in the plane of the matrix surface. Cyclic uniaxial stretching (10%, 1 Hz) causes the stress fibers oriented toward the stretch direction to preferentially disassemble, resulting in the gradual accumulation of stress fibers perpendicular to the direction of stretch. Values for the parameters k_0 and k_1 of $1.0\times10^{-6}\,s^{-1}$ and 2.5×10^5, respectively, were estimated previously to describe the time course of stress fiber alignment in confluent bovine aortic endothelial cells subjected to 10% cyclic uniaxial and equibiaxial stretches at 1 Hz (Kaunas and Hsu, 2009). For cyclic equibiaxial stretch, simulations using the same parameters resulted in a uniform distribution of stress fibers as observed in experiments.

2.3. JNK activation model

The mitogen-activated protein kinases (MAPKs) are a family of proteins, including extracellular signal-related kinase (ERK), JNK and p38, that are activated by extracellular signals including growth factors and integrin ligands (Lodish et al., 2008). All members of the MAPK family are serine/threonine kinases that are activated in the cytosol and translocate into the nucleus to regulate transcription. Several proteins, including FAK, paxillin, p130Cas, Crk, and Ras are each components of pathways identified as leading to integrin-mediated activation of both ERK and JNK (Almeida et al., 2000; Chrzanowska-Wodnicka and Burridge, 1996; Clark and Brugge, 1995; Igishi et al., 1999). JNK and ERK are each activated through phosphorylation of threonine and tyrosine residues (Sanchez et al., 1994; Tournier et al., 1997) and deactivated by the removal of either phosphate group via dual specificity phosphatases (Camps et al., 2000).

Instead of focusing on the details of each potential protein in the pathway, the aim of our model was to gain quantitative insight into the overall performance of stretch-induced JNK activation. Due to a lack of detailed information available regarding the kinetics of the pathways leading to JNK activation and due to the similarities between ERK and JNK activation by integrin ligation, we assumed a collective behavior similar to that reported by Asthagiri et al. (1999). We expressed the rate of JNK phosphorylation using simple first-order kinetics,

$$\frac{dC_{pJNK}}{dt} = -\frac{dC_{JNK}}{dt} = k_f C_{JNK} - k_r C_{pJNK} \tag{2}$$

where k_f and k_r are the rate parameters characterizing the rates for phosphorylation and dephosphorylation, respectively, and C_{JNK} and C_{pJNK} are the concentrations of the unphosphorylated and phosphorylated forms of JNK, respectively. Asthagiri et al. (1999)