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Effects of stress fiber contractility on uniaxial stretch guiding mitosis orientation and stress fiber alignment

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ABSTRACT

It has been documented that mitosis orientation (MO) is guided by stress fibers (SFs), which are perpendicular to exogenous cyclic uniaxial stretch. However, the effect of mechanical forces on MO and the mechanism of stretch-induced SFs reorientation are not well elucidated to date. In the present study, we used murine 3T3 fibroblasts as a model, to investigate the effects of uniaxial stretch on SFO and MO utilizing custom-made stretch device. We found that cyclic uniaxial stretch induced both SFs and mitosis directions orienting perpendicularly to the stretch direction. The F-actin and myosin II blockages, which resulted in disoriented SFs and mitosis directions under uniaxial stretch, suggested a high correlation between SFO and MO. Y27632 (10 μM), ML7 (50 μM, or 75 μM), and blebbistatin (50 μM, or 75 μM) treatments resulted in SFO parallel to the principle stretch direction. Upon stimulating and inhibiting the phosphorylation of myosin light chain (p-MLC), we observed a monotonic proportion of SFO to the level of p-MLC. These results suggested that the level of cell contraction is crucial to the response of SFs, either perpendicular or parallel, to the external stretch. Showing the possible role of cell contractility in tuning SFO under external stretch, our experimental data are valuable to understand the predominant factor controlling SFO response to exogenous uniaxial stretch, and thus helpful for improving mechanical models.

1. Introduction

Mechanical forces are widely involved in regulating basic cellular functions, including proliferation, differentiation, adhesion, and migration (Orr et al., 2006; Wang and Thampatty, 2006). However, few studies show how these mechanical forces impact mitosis orientation (MO), a crucial process in embryogenesis, organogenesis, cell differentiation, and tissue injury recovery. It has been reported that intracellular cues and extracellular microenvironments are involved in the spindle positioning process. Independent research groups have demonstrated that stress fibers (SFs, comprised of F-actin and myosin) and integrin-mediated cell adhesion to the extracellular matrix (ECM) are essential to the MO determination (Fernandez-Minan et al., 2007; Toyoshima and Nishida, 2007; Woolner et al., 2008; Zhou et al., 2010). In consideration of these findings and the fact that mechanical forces induce stress fiber orientation (SFO; Takemasa et al., 1997; Wang, 2000; Kaunas et al., 2006), we hypothesized that the mechanical microenvironment may guide MO via its effect on SFO.

With investigation of this hypothesis, we should take into account a well documented but puzzling phenomenon, whereby external stretch reorients SFs in vascular endothelial cells and fibroblasts (Kito et al., 2000; Wang et al., 2001, 2004; Neidlinger-Wilke et al., 2002; Birukov et al., 2003). To address a biomechanical issue, mathematical models help elucidate the complex relations between SFO and different patterns of stretch (De et al., 2007, Deshpande et al., 2006; Hsu et al., 2009; Stamenović et al., 2009). Based on different criteria, such as maintaining local strain in the surrounding matrix or SF, or attaining a global minimum energy, different models predicted that SF contractility, Poisson's ration of the substrate, or the strain frequency are the predominant parameters controlling SFO response to the exogenous uniaxial stretch, respectively. These predictions provide valuable insight into how cells sense and respond to external stretch, yet conflicts remain in these models and we still do not fully understand what factors determine the stretch-induced SFO and MO. More experimental data should be valuable to understand the predominant factor controlling SFO response to the exogenous uniaxial stretch.

SFs, which represent the main contractile apparatus in non-muscle cells, terminate at focal adhesions. SF contraction is achieved by actin–myosin interactions, which are regulated by myosin light chain kinase (MLCK), Rho/Rho-kinase, or Protein kinase C (PKC)

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