C. R. Mecanique 342 (2014) 334–346

Contents lists available at ScienceDirect

Comptes Rendus Mecanique

www.sciencedirect.com

Frontiers of micro and nanomechanics of materials: Soft or amorphous matter, surface effects

Cell polarization energy and its implications for cell migration

Yuan Zhong, Shijie He, Chunying Dong, Baohua Ji *, Gengkai Hu

Biomechanics and biomaterials laboratory, School of Aerospace Engineering, Beijing Institute of Technology, Beijing 100081, China

ARTICLE INFO

Article history:
Received 26 August 2013
Accepted 11 November 2013
Available online 24 April 2014

Keywords:
Cell shape
Cell polarity
Matrix rigidity
Cell adhesion
Driving force of cell migration

ABSTRACT

Cells usually have a polarized shape in directional cell migration. This cell polarity may result from external cues, such as a gradient of chemo-attractants (chemotaxis), or a gradient of mechanical properties of substrate (durotaxis), and it can also arise from internal cues so that the cells self-polarize spontaneously and maintain the polar motile state for a long time. However, the mechanisms that control cell polarization have not been fully understood, and particularly, the relationship between the polarized shape and cell migration behaviors is not yet clear. In this study, we propose an energy model to study the cell polarization energy by considering the effect of matrix rigidity, cell shape, and organization of the cytoskeleton. We then propose a parameter called "motility factor" for depicting the relationship between the cell shape and the driving force of cell migration. We demonstrate that the fibroblast-like cell shape and keratocyte-like shape both have an optimal polarization angle corresponding to the most stable cell shape. Fibroblast-like cell shape also has an optimal tail length of the polarization. Furthermore, we find that the cell free energy biphasically depends on the matrix rigidity, i.e. that there is an optimum matrix rigidity for the most stable shape. And the motility factor also biphasically depends on the matrix rigidity, but the trends of the dependence are opposite to that of cell's free energy, which implies an optimum matrix rigidity for the highest speed. The optimum matrix rigidity for the most stable cell shape and that for the highest cell speed are consistent, suggesting that the most stable cell shape is favorable to the fastest cell migration. This study provides important insights into the relationship between cell polarization shape and cell migration behaviors.

1. Introduction

Adhesive cells often have specific polarization shapes during their directional migration. The diverse migratory behaviors of various cell types are manifested by a spectrum of their different shapes [1]. Fibroblast and keratocyte are two typical adhesive cells that were intensively studied in the past decades. In the non-polarized state, the two cells are both approximately disk-like [2–4]. But in the polarized state, fibroblasts have a spindle-like shape with a long "tail" and keratocytes have a "crescent"-like shape with two flank-like rears [1,5,6]. The transformation from the non-polarized state to the polarized one is accompanied by changes of the cell's shape and structure, such as re-organization of cytoskeleton and variation of protrusion and adhesive regions [3,7–11]. During cell polarization, the mechanical factors should play important roles in this symmetry-breaking event.

* Corresponding author. Tel.: +86 10 68918309.
E-mail address: bhji@bit.edu.cn (B. Ji).

http://dx.doi.org/10.1016/j.crme.2014.02.006
1631-0721/

Existing studies suggest that the cell may adopt a specific polarization shape for a minimum free energy. Mogilner and coworkers [12] proposed a thermodynamic model for analyzing the polarization energy of keratocytes by considering thermodynamic works by various intracellular forces. Vianay et al. [13] studied cell spreading on a protein lattice based on the principle of minimum energy, suggesting that the cell shapes were in thermodynamic metastable states. Ujihara et al. [14] simulated the change of cell shape and the cytoskeleton deformation under tensile stretching by modeling the cell as a spring network based on the minimum-energy concept. Du et al. [15] studied the effect of polymerization and depolymerization of actin filaments on cell shape and cell migration by considering the interaction between molecular motors and actin filaments as well as free energy of cell membrane. In prior studies, surface energy and volume work are the main energy components that had been considered in the modeling of different cell types [16,17].

Cell migration behaviors intensively depend on the matrix rigidity. Experiments showed a biphasic relationship between the velocity of cell migration and the rigidity of matrix [18,19]—cells migrate with low velocity on either soft or hard matrix while with a peak speed on the matrix of intermediate rigidity. The polarization shape of cells also depends on the matrix rigidity—the higher the matrix rigidity, the larger the aspect ratio of fibroblasts [3,20]. The aspect ratio of cell is defined by the ratio L_x/L_y, where L_x and L_y are the effective length and width of cell, respectively, and x is along the direction of cell migration, thus the shape of the fibroblasts is getting more spindly with increasing matrix rigidity.

To understand the cell migration behaviors, many mechanical models have been developed. Mogilner and coworkers [21] did pioneering works in modeling actin dynamics in cell migration, and also gave a comprehensive review of existing models [22]. Dokukina and Gracheva [23] developed a FEM-based model for studying the relationship between cell speed and matrix rigidity. Sarvestani [24] predicted a biphasic dependence of cell speed on matrix rigidity by considering the gradient of the density of adhesion molecules and stall force from the cell front to the cell rear. Lee et al. [25] developed a so-called “graded radial extension” (GRE) model for keratocyte by considering a graded distribution of extension and retraction rates along cell edge. Keren et al. [26] studied the role of treadmill of the actin network on the cell shape and migration based on the GRE model, and Barnhart et al. [27] further consider the effect of adhesion strength on cell shape and migration speed.

Although many efforts have been paid to either studies of cell polarization or those of cell migration, the knowledge of the relationships between the polarization shape and the migration behaviors is still lacking. The effect of matrix rigidity on cell polarization was not fully understood either. It is necessary to study the matrix-rigidity-dependent cell polarization shape and the shape-dependent cell migration behaviors for a comprehensive understanding of the relationship between cell polarization and cell migration. In this study, we first propose a thermodynamic model for cell polarization based on Mogilner’s concept [12] and consider the effect of matrix rigidity on cell shape. Here we study two kinds of cells—fibroblast and keratocyte—by focusing on the fibroblast cell and by comparison of the two kinds of cells. Then we propose a parameter called “motility factor” to quantitatively describe the driving force of cell migration. At last, the relationship between cell polarization shape and cell migration behavior is discussed.

2. Models of cell polarization

2.1. The non-polarized state

For the non-polarized state, both fibroblast and keratocyte have disk-like cell shape [2,3,8,12] (Fig. 1). The actin filament and myosin are assumed to be distributed homogeneously in the cell based on experimental observations [2]. Most of actin filament networks near the cell membrane make isotropic polymerization, producing an isotropic protrusion force. The total protrusion force is assumed to be constant [12]. Generally, cytoplasmic pressure σ_{mem} applied on the cell membrane is isotropic in the cell membrane plane. The actin filament bundle distributed at the cell’s periphery may form by cytoplasmic retraction or centripetal cytoplasmic flow [28,29]. The initial radius of the cell before polarization is R_0. The cells without polarization have a free energy E_0 that is called the initial free energy.

2.2. The polarized state

The transformation of a cell from the non-polarized state to the polarized one is produced by the intracellular forces. Before polarization, the actin filament network near the cell membrane provokes an isotropic polymerization, producing an isotropic protrusion force. In the polarization process, while polymerization is kept at the cell front, that at the cell rear stops, replaced by depolymerization [8]. Thus, the equilibrium of the cell membrane breaks, and a concave cell shape forms at the cell rear with the cytoplasmic retraction or centripetal cytoplasmic flow [29].

For a clear description in the model, we use superscript “f” for the variables and parameters of fibroblast and “k” for those of keratocyte, and those without superscript are applied to both cells.

For fibroblast, the cell shows an arc-like convex front edge and a characteristic long tail at the cell rear [1]. This typical shape can be described by the polarization angle φ^{f}, radius of cell front R^{f} and length of cell tail L^{f} (see Fig. 1 & 2). In our model, the protrusion force at the cell front is considered as constant for the expansion of the cell leading edge, while the protrusion force at the cell rear concentrates at the endpoint and helps the formation of the cell tail. At the cell periphery, the surface tension $\lambda_{\text{B}}^{\text{f}}$ is generated by the contractile myosin of the actin filament bundle, keeping the concave shape at the cell rear under pressure σ_{mem} [16,28]. The actin filaments are re-orientated to align along the migrating direction of