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Modeling mechanosensing and its effect on the migration and proliferation of adherent cells

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Abstract

The behavior of normal adherent cells is influenced by the stiffness of the substrate they are anchored to. Cells are able to detect substrate mechanical properties by actively generating contractile forces and use this information to migrate and proliferate. In particular, the speed and direction of cell crawling, as well as the rate of cell proliferation, vary with the substrate compliance and prestrain. In this work, we present an active mechanosensing model based on an extension of the classical Hill's model for skeletal muscle behavior. We also propose a thermodynamical approach to model cell migration regulated by mechanical stimuli and a proliferation theory also depending on the mechanical environment. These contributions give rise to a conceptually simple mathematical formulation with a straightforward and inexpensive computational implementation, yielding results consistent with numerous experiments. The model can be a useful tool for practical applications in biology and medicine in situations where cell–substrate interaction as well as substrate mechanical behavior play an important role, such as the design of tissue engineering applications.

Keywords: Cell–matrix interaction; Mechanotaxis; Computational model; Mechanobiology

1. Introduction

Research on cell migration and proliferation has drawn the attention of the scientific community during the last decades. It has now become a leading interdisciplinary research field that demands the collaboration of cellular biologists with experts from other disciplines, such as computer modeling and imaging, and biomaterial and mechanical engineering [1]. The relevance that cell motility has gained in biology research is due to its major role in several physiological and pathological processes, e.g. morphogenesis, inflammatory response, wound healing and tumor metastasis [2]. Cell migration and proliferation are also of significant interest in the field of tissue engineering. In fact, the primary function of a scaffold in tissue engineering is to serve as a substrate to which cells can attach, grow and maintain differentiated functions, and all of these processes can be strongly influenced by the scaffold microstructure and mechanical properties, as well as the biological and chemical properties of its surface [3].

Cell movement is guided by input signals from the surrounding environment in order to achieve an appropriate organization of cells and production of extracellular matrix (ECM) within tissues and organs. Migration, in response to gradients of dissolved or surface-attached chemicals, light intensity or electrostatic potential, has been studied for years [4]. More recently, the influence of the stiffness and topography of the ECM or substrate that adherent cells are anchored to has been investigated [4–6]. Among other important results, it has been found that cells crawl better

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on stiffer and more strained substrates, phenomena that have been defined as *durotaxis* and *tensotaxis*, respectively [7]. Moreover, it has been found that the stiffness of the substrate also directs cell proliferation, the proliferation rate being markedly reduced on more compliant substrates [8].

The immediate question that emerges is how are cells able to sense ECM flexibility or prestrain? In the last few years, it has become clear that adherent cells anchor to a substrate and then exert contractile forces in order to explore the properties of their environment, what is a part of the so-called process of *mechanosensing* [9]. These active forces are primarily generated by the actomyosin contractile machinery and transmitted to the ECM by means of transmembrane proteins of the integrin family in so-called focal adhesions [10]. The cytoplasmic domains of integrins are linked to the actin cytoskeleton (CSK) by a network of adapter proteins that form a submembrane plaque [11]. It has been found that cells exert higher contractile forces and show larger stable focal adhesions on stiffer substrates [12–14]. Moreover, the application of external stress/strain on the cell also stimulates focal adhesion formation and increases the tension that the submembrane plaque withstands [15,16]. This tension can trigger molecular reorganization at the adhesion sites or alterations in the conformation of plaque proteins or integrins. That is the reason why the integrin-mediated submembrane plaque tension-dependent mechanism has been hypothesized as a possible mechanosensitive path [10].

In addition to this extensive experimental research, mathematical models and computational simulations can also provide some insight into these matters [17–19]. Efforts have been addressed to the study of mechanosensing, and several models based on mechanics [20], thermodynamics [21] or the dynamics of focal adhesions [22] have been proposed. Cell migration modeling has received considerable attention, with some works aiming at reproducing the influence of chemical and mechanical properties of the substrate on cell locomotion [23,24].

In this paper, we present a model that makes predictions about mechanosensing and cell migration and proliferation. We show how active mechanosensing, albeit resulting from complex molecular processes, can be explained by the interaction of the mechanical behavior of the CSK components, the actomyosin contractile system and the ECM compliance. Applying equilibrium conditions to this simple scheme, equivalent to Hill's model for active muscle behavior [25], we are able to explain many experimental findings obtained for adherent cells on soft substrates. With regard to cell migration, we propose modeling the time and spatial evolutions of cell concentration through the classical transport equation within the framework of continuum mechanics. Our contribution in this direction consists in deriving an expression for the cellular flux from thermodynamic arguments, so that the input of mechanical signals received by individual cells through active mechanosensing is taken into account. Furthermore, the variation of the rate of proliferation depending on the mechanics of the ECM observed experimentally [8] has been also modeled.

The resulting continuum formulation has been implemented in a finite element framework, and computational simulations of cell migration on two-dimensional (2D) gradient-compliant and gradient-strained substrates have been performed, obtaining results that agree with several experimental observations. In order to predict cell–ECM interaction and the influence of the mechanical environment upon cell locomotion and proliferation in a specific biological phenomenon, e.g. fibroblast locomotion in wound healing, mesenchymal cell migration at the interface of a recently placed dental implant or endothelial cell organization in vasculogenesis and angiogenesis, it would be necessary to integrate every particular biological process of interest into this general model. In particular, the model is specifically suited for rational design of tissue engineering applications, since it allows one to understand the interaction between the mechanical state of the environment and cell behavior.

2. Mechanosensing model

The cellular elements that carry out a relevant function in the mechanics of cell mechanosensing and that have been considered in our model are the actin bundles, the actomyosin contractile apparatus and the passive mechanical strength of the rest of the body cell, whose main contribution comes from the CSK microtubules and the membrane (Fig. 1A). The cytoplasmic CSK is linked with the external ECM through focal adhesions and transmembrane integrins that are assumed perfectly rigid for our purposes. This scheme agrees with the tensegrity hypothesis [26], since tensile forces generated in the actin CSK are balanced by the compression of the microtubules and the external substrate. Finally, external forces are also taken into account, being another possible cause of the deformation of the substrate and cell. Note that this model can be applied to adherent cells, irrespective of the nature of their actual environment: plated on elastic substrates, cultured on hydrogels or on the surface of a scaffold or attached to the ECM of a connective tissue. Consequently, the expressions ECM and substrate will be used henceforth without distinction.

Even though the above suggested model, depicted in Fig. 1B, is one-dimensional, if isotropy for the contractile forces exerted by cells is assumed (which, although not the actual case, is sufficiently approximate for the aim of this work and useful in the interests of simplicity), one can interpret forces in each branch of the scheme of Fig. 1B as octahedral or hydrostatic stresses, and the change of length of each element as its corresponding volumetric strain [27]. In such a case, the characteristic value of each spring can be identified with the volumetric stiffness modulus of the representing element. Forces in each branch of the model then have a clear physical interpretation: p_c is a measure of the mean contractile stress generated internally by the myosin II machinery and transmitted through

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