Substrate stiffness dependent cell migration behaviors

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Summary Cell migration behaviors play key roles in both physiological and pathological processes. Experimental observations showed that cell migration behaviors are very sensitive to the substrate rigidity. However, the underlying mechanisms about how substrate stiffness influences the cell migration behaviors have not yet been understood. In this study, a FEM-based simulation method was developed by modelling the dynamics of cell adhesion at cell front, de-adhesion at cell rear and movement of cell body under the cell contractile force. Our simulations showed that cell migration speed biphasically depends on the matrix stiffness and this dependence can be tuned by the stiffness gradient. The underlying mechanism is that the matrix stiffness can influence the balance of competition of stability of cell adhesion between the cell front and cell rear, which consequently control the driving force of cell migration. The rigidity gradient will bias this competition which allows cell to exhibit a durotaxis behavior.

Introduction

Cell migration takes crucial roles in many physiological and pathological processes, such as embryogenesis, wound healing, immune defence, and cancer metastasis, etc [1,2]. It is a complex process involving the dynamics of cell adhesion, cytoskeleton remodelling, and the cell-matrix interaction. Experimental observations showed that the mechanical factors could have significant effects on cell migration. For example, the speed of cell migration can be regulated by many parameters such as the rigidity of matrix as well as the concentration of adhesion proteins [3,4]. Because of the complexity of cell migration process, a quantitative study connecting different parameters using a rational mathematical and mechanical modelling is highly needed.

Previous modelling works on cell migration were either relying on the assumption of rigidity dependent asymmetric cell contractile force distribution or rigidity dependent asymmetric integrin density distribution, which were lack of rigorous mathematical and physical basis. Here we assume that the stabilizing to disruptive transition of dynamics of focal adhesion complex (FAC) should be crucial to cell migration behaviors, and the matrix rigidity could influence the dynamic state transition of FAC. This study is aimed to explain the underlying mechanisms that how the stiffness of matrix, cell shape and rigidity gradient influence the cell migration behaviors. Furthermore, a parameter called "motility factor" was suggested for quantitatively describing the driving force of cell migration.

Method

To simulate the cell migration behaviors, we developed a FEM model by considering the stability of focal adhesion complex (FAC) and the translation of cell body driven by cell contractile force, which can be influenced/determined by substrate stiffness, stiffness gradient and cell shape. In our model, both cell and matrix are deformable, and the contractile force of stress fiber can be transferred to matrix and the deformation of matrix can influence force distribution of cell via FACs. Therefore, the cell-matrix interaction is fully considered. The matrix was modelled as a two-dimensional lattice network of elastic rods in a regular triangular lattice.

We suggested that the dynamics of focal adhesion complex should play important roles in cell migration. For instance, the formation of FAC at the front of cell, and the disassembly of FAC at the rear of cell, which depends on its unique feature of stabilizing to disruptive transition. According to our previous studies [5,6], a phenomenological model was introduced for describing the dynamics of the FAC under external loading.

The real cell geometry of keratocytes and fibroblasts was used in the cell migration simulation. Firstly, the contractile force in cell that applied on FACs was calculated. Secondly, the stability of FACs was then predicted. Thirdly, the driving force of cell migration was calculated. In this study, the breaking of cell symmetry is caused by the disassembly of FACs at the cell rear, which then generates the driving force for cell migration.

Results

The effect of stiffness of matrix on cell migration speed is shown in Fig.1, which exhibits a maximum cell migration speed at an intermediate rigidity of matrix, i.e., the cell migration speed biphasically depends on the substrate stiffness, which is consistent with many experimental results.

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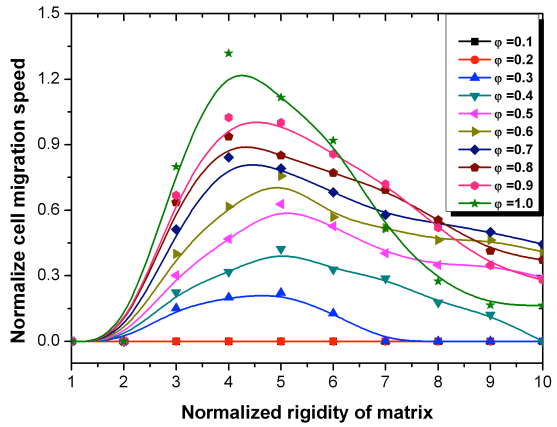

Figure 1 Substrate stiffness dependent cell migration speed

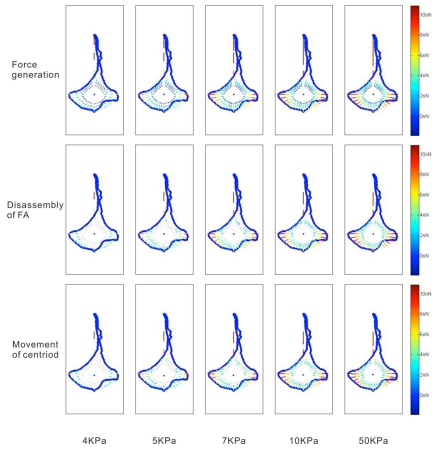

Figure 2 Contractile force distribution at different substrate stiffness

To understand the mechanisms of the biphasic behaviors of cell migration, we draw the force distribution in cell at different substrate stiffness, which is shown in Fig.2 for fibroblast. As we can see, at low rigidity of matrix, the adhesion strength is so weak that stable focal adhesion complexs can hardly form at cell front, only generating very small contractile pulling force and therefore producing low cell migration speed. At this regime of rigidity, the cell migration speed is controlled by the FAC formation. In contrast, at high rigidity of matrix, although the contractile force at cell front is increased by the formation of strong FACs, it becomes difficult for cell to make de-adhesion at the cell rear, leading to the decrease of cell migration speed. At this regime, the migration speed is controlled by the rupture of FACs. At an intermediate matrix stiffness, the migration speed achieves the maximum value because of the relatively larger contractile force at cell front compared with that at soft matrix, and at the same time relatively weaker adhesion at cell rear compared with that at the hard matrix, which make cell produce larger driving force that drives the cell body to move faster. Therefore, the biphasic fashion of rigidity sensing of cell migration is caused by the competition between the formation of FACs at cell front and the rupture of FACs at cell rear.

Discussion

In this study, the cell migration behaviors were studied by modelling typical dynamic process of cell migration, i.e., focal adhesion complex formation at cell front, de-adhesion at cell rear, and cell body moving forward under contractile force, in a FEM-based simulation framework. We showed the dynamics of FAC is the key player in the orchestration of adhesion formation at the cell front, and de-adhesion at the cell rear. The effect of a few parameters on the cell migration behaviors were studied, including the rigidity of matrix, the rigidity gradient, and the cell shape. We found that the matrix stiffness can influence the competition of the stability of FACs between those at the cell front and those at cell rear. At a comparably softer matrix, the stability of FACs at the cell front will be enhanced by the increase of the matrix stiffness, therefore it dominate the driving force of cell migration. In contrast, for the comparably stiffer matrix, the increase of the matrix stiffness will enhance the stability of FACs at cell rear, therefore the FACs at the rear will dominate the driving force of cell migration. The rigidity gradient will bias this competition. That is, positive gradient (in the direction of cell migration) will enhance the cell migration, while the negative gradient will weaken the cell migration. Furthermore, we showed the cell shape is also a key factor for cell migration, because it controls the contractile force distribution in the cell, therefore influences the driving force for cell migration. A parameter called “motility factor” was suggested for quantitatively describing the effect of matrix properties and cell shape on cell migration behaviors. We showed that this parameter could effectively explain the biphasic dependence of cell migration speed on the matrix stiffness.

References

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