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Stabilizing to disruptive transition of focal adhesion response to mechanical forces

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ABSTRACT

Strong mechanical forces can, obviously, disrupt cell–cell and cell–matrix adhesions, e.g., cyclic uniaxial stretch induces instability of cell adhesion, which then causes the reorientation of cells away from the stretching direction. However, recent experiments also demonstrated the existence of force dependent adhesion growth (rather than dissociation). To provide a quantitative explanation for the two seemingly contradictory phenomena, a microscopic model that includes both integrin–integrin interaction and integrin–ligand interaction is developed at molecular level by treating the focal adhesion as an adhesion cluster. The integrin clustering dynamics and integrin–ligand binding dynamics are then simulated within one unified theoretical frame with Monte Carlo simulation. We find that the focal adhesion will grow when the traction force is higher than a relative small threshold value, and the growth is dominated by the reduction of local chemical potential energy by the traction force. In contrast, the focal adhesion will rupture when the traction force exceeds a second threshold value, and the rupture is dominated by the breaking of integrin–ligand bonds. Consistent with the experiments, these results suggest a force map for various responses of cell adhesion to different scales of mechanical force.

1. Introduction

Cells sense and respond to forces from either cell contractility or extracellular environment through focal adhesions (FAs) (Galbraith and Sheetz, 1998; Geiger et al., 2001; Janmey and McCulloch, 2007; Katsumi et al., 2004). As mechanosensory 'device' and signaling 'center' of cell, FAs play central roles in the cellular decision-making mechanisms. FAs provide cells the necessary force transmission pathways to "feel" their microenvironment through actin–myosin contractions. However, currently it is still elusive for the precise mechanisms of mechanosensing and mechanotransduction between inside and outside of cells. Two typical phenomena are of particular interest. One is that the pulling force by micropipette or stretching can induce growth of FAs (Balaban et al., 2001; Bershadsky et al., 2003; Riveline et al., 2001; Tan et al., 2003), and the second one is that the cyclic stretching can cause cell reorientation (Buck, 1980; Dartsch and Hammerle, 1986; Jungbauer et al., 2008; Kaunas et al., 2005; Moretti et al., 2004; Neidlinger-Wilke et al., 2001, 2005; Wang et al., 1995). These experiments showed that cell has very different, apparently contradictory responses to forces, i.e., the force can cause both growth and rupture of FAs.

Motivated by the above intriguing properties of FAs, many theoretical works were conducted for understanding of the underlying mechanisms of the FA mechanosensitivity. Nicolas and coworkers (Nicolas et al., 2008, 2004 ; Nicolas and Safran, 2006) developed the first theoretical model for the force-induced FA growth. They proposed that the origin of the growth is the deformation of the stressed FA. They assumed that a local tangential stress induces a compression at the front and an expansion at the back of FA, which causes different growth velocities at the front and back. They found that the FA grows only within a specific range of traction. Shemesh et al. (2005) studied the force-induced FA growth with a different approach. They assumed that the FA can grow under the tension stress throughout the entire FA region, and the growth was achieved by the assembly of adhesion proteins induced by the chemical potential decrease due to the expansion deformation of the FA.

Besides the force-induced growth phenomenon of FAs, it is worthwhile to note the force-induced instability of FAs. For example, cells adhered on a cyclically stretched substrate tend to reorient themselves away from the stretching direction (Buck, 1980; Dartsch and Hammerle, 1986; Jungbauer et al., 2008; Kaunas et al., 2005; Neidlinger-Wilke et al., 2001, 2005; Wang et al., 1995). Instead of the cell adhesion being

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strengthened (e.g., force induced growth of FAs), Dartsch and Hammerle (1986) found that cells begin to reorient themselves when the stretch amplitude is larger than a threshold value (ca. 2%). The larger the stretch amplitude, the more the cells reorient (Neidlinger-Wilke et al., 2001). To understand the underlying mechanisms of cell reorientation under dynamical external load, many phenomenological models have been developed, such as the elasticity model (Wang et al., 1995), the contact mechanics model (Chen and Gao, 2006), and the force dipole model (De and Safran, 2008; De et al., 2007, 2008). Gao and coworkers (Qian et al., 2008; Wang and Gao, 2008) developed a coupled stochastic-elastic model by which they found there is an optimal FA size for the stability of the FA. Kong et al. (2008) studied the stability of FAs by analyzing the stochastic bond formation and rupture in a cluster of integrin–ligand bonds under cyclic stretching with a new microscopic model.

Although previous studies have provided many insights into the force-induced FA growth and instability of cell adhesion, less is known about the connections between the two seemingly paradoxical mechanical behaviors and about how to model them in a unified theoretical frame. In this study, we propose that the different mechanical responses of cell adhesion to forces can be understood from molecular level through a microscopic model. The content of the present paper is organized as follows. In the next section, we introduce the microscopic model that considers the clustering dynamics of integrin with associated linker proteins and the binding dynamics of integrin–ligand bonds by treating the FA as an adhesion cluster. The dynamics of integrin complex clustering and the integrin–ligand binding are simulated by including both the integin–integrin interaction and the integrin–ligand interaction in the cluster model. The numerical scheme is introduced in the third section. Numerical results of the force dependent responses of FAs are explained by analyzing the mean fraction of integrin–ligand bonds in the fourth section. Discussions and conclusions are made in the last section.

2. A microscopic model

Focal adhesions are spot-like regions of proteins connecting the cytoskeleton to ECM as shown in Fig. 1A. In this study, the focal adhesion is modeled as a cluster of integrins and associated linker/adaptor proteins, called integrin complex units (ICU, see Fig. 1B), which are linked to ECM through integrin–ligand bonds. The cytoplasmic part of the aggregation of ICU proteins forms the adhesion plaque structure which is connected with the cytoskeleton via stress fiber. According to the previous studies (Besser and Safran, 2006; Nicolas et al., 2008, 2004; Nicolas and Safran, 2006), the microscopic picture of growth or shrinkage of FA might be illustrated as following: when the force is applied to or released from the FA, the ICU proteins will attach to or detach from it (see Fig. 1C). That is, the growth and shrinkage of FA can be modeled as addition or subtraction of ICU proteins, respectively. At the same time, the integrin–ligand bonds are stochastically formed and ruptured under the thermal fluctuation (see Fig. 1D), while the presence of external force will make the bonds vulnerable to rupture. More details about the microscopic model are given in Supplementary Material S1 & S2.

With all the scenarios above in the mind, we consider two kinds of chemical reaction processes, i.e., integrin clustering and integrin–ligand bond forming, in the adhesion cluster model, to study the collective behaviors of ICU proteins under the forces of different scales, aiming to reveal the underlying mechanisms of the force dependent responses of FA. In this study, the force dependent integrin clustering is described by a forward rate:

$$g_{on} = g_{on}^0 \exp(-\Delta\mu/k_BT), \tag{1}$$

where g_{on}^0 is the forward rate constant, k_BT is the thermal energy, and $\Delta\mu$ is the local chemical potential reduction, which is related to the traction force by (Hill and Kirschner, 1982; Shemesh et al., 2005)

$$\Delta\mu = \Delta\mu_0 - \gamma l_0, \tag{2}$$

where $\Delta\mu_0$ is the difference of chemical potentials between aggregated and nonaggregated integrin complex units in the absence of traction force, l_0 is the original molecular length of the ICU (Fig. 1C), and l_0 is equal to the distance between two integrins along the loading direction before their deformation (see Fig. 1D). γ is the traction force acted on one integrin complex unit and can be represented as $\gamma = \tau_{FA} l_0^2$, in which τ_{FA} is the traction per unit area. Eq. (2) can be derived in a similar spirit of previous studies (Hill and Kirschner, 1982; Shemesh et al., 2005) as follows. The chemical potential change of one single aggregated molecule is

$$d\mu = l\, d\gamma, \tag{3}$$

where l is the molecular length. According to the continuum mechanics, the traction force along the surface of FA will only induce shear deformation which cannot change the size of FA, i.e., $l = l_0$. Neglecting the elastic shear deformation energy of FA, we can get Eq. (2) by integrating Eq. (3). $\Delta\mu_0$ is regarded as the minimum energy to trigger the clustering of ICUs, which is estimated at the order of tens of k_BT. On the other side, the deaggregation of FA proteins is characterized by a reverse rate g_{off}. For simplicity, we assume that g_{off} does not depend on the traction force as a constant. Eqs. (1) and (2) show that the application of traction force can decrease the local chemical potential and then drive the integrin clustering.

On the other side, the traction force will also impair the stability of integrin–ligand bonds between cell and ECM substrate by developing internal tension in these adhesion bonds (Kong et al., 2008). The dynamics of integrin–ligand binding can be described by another chemical reaction, characterized by forward rate k_{on} and reverse rate k_{off}, as shown in Fig. 1D. The reverse rate k_{off} is commonly described by the Bell model (Bell, 1978) as

$$k_{off} = k_{off}^0 \exp(f\lambda/k_BT), \tag{4}$$

where k_{off}^0 is the reverse rate constant, f is the bond force and λ is the compliance length, which can be viewed as the range of the energy well that defines the bound state. The forward rate k_{on} is assumed to be independent on the bond force and taken as a constant. The bond force deforms the integrin–ligand bonds and lowers the energy barrier for bond rupture. By assuming that the applied traction is equally sharing among all the bonds (Erdmann and Schwarz, 2004a, 2004b), the bond force f can be obtained according to the mechanical equilibrium of the FA under the traction force and bond force along the horizontal direction (see Fig. 1):

$$f = \frac{1}{n_1/n_2}\frac{\gamma}{\cos\theta}, \tag{5}$$

where θ is the tilting angle of integrin–ligand bonds due to the traction, n_1 is the number of closed bonds, and n_2 is the number of aggregated ICUs in the adhesion plaque (or total bond numbers). n_1/n_2 is equal to the probability of closed state of bonds. We assume that the bonds are linear elastic, i.e., $f = k\Delta L$, where k is the stiffness of integrin–ligand bonds. The relationship between θ and the deformation of bonds is

$$\sin\theta = \frac{L}{L+\Delta L}, \tag{6}$$

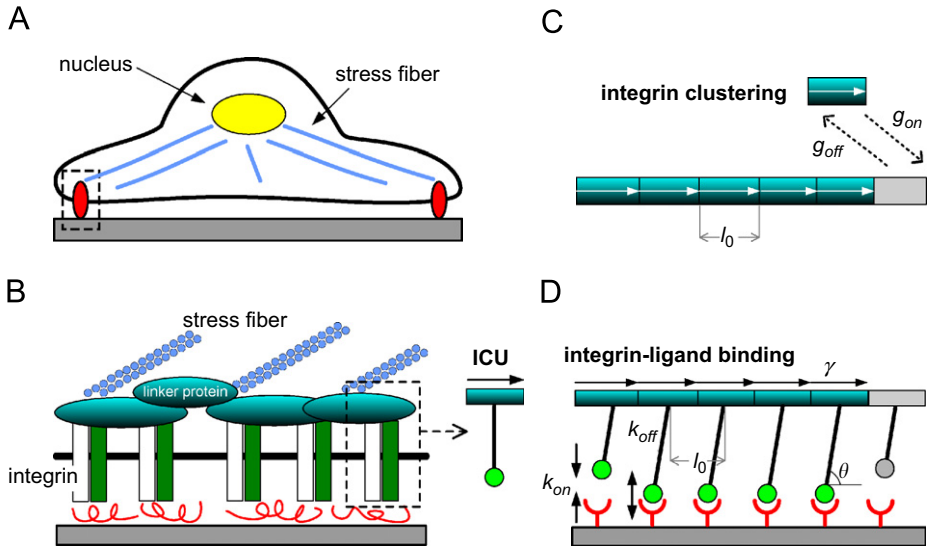

Fig. 1. A microscopic model for the FA. (A) An adhered cell with FAs at the cell-ECM interface. (B) Schematic illustration of microscopic structure of the FA, where the interior domains of integrins attach to actin stress fibers via linker proteins, such as vinculin and talin, while the exterior domains of integrins bind with ligands to form integrin–ligand bonds between cell surface and substrate. The dashed rectangle indicates an integrin with associated linker proteins, which is modeled as an integrin complex unit (ICU). (C) Schematic illustration of attachment or detachment of integrin complex units from the adhesion plaque. (D) Schematic illustration of bond forming and breaking between the integrins and ligands.

The tilting angle θ and bond force f can be calculated by solving the force equilibrium equation (Eq. 5) and geometrical equation (Eq. 6) simultaneously. The total traction force applied on the FA is proportional to the number of aggregated integrin molecules. The evidence is that experimental measurements of the forces applied on FAs showed that there is a linear relationship between the force and the area of the focal adhesion (Balaban et al., 2001).

3. Numerical methods

The clustering dynamics of ICUs and binding dynamics of integrin–ligand bonds were simulated by using Monte Carlo simulation with the Gillespie first-reaction algorithm (Gillespie, 1976, 1977). The stochastic dynamics of integrin clustering and the integrin–ligand bond binding, modeled as two kinds of bi-directional reactions, can each be described by the one-step master equation:

$$\frac{dP_i}{d\tau} = r_{i+1}P_{i+1} + f_{i-1}P_{i-1} - (r_i + f_i)P_i \tag{7}$$

where $P_i(\tau)$ is the probability function at time τ. r_i and f_i are the total reverse and forward rates of the reaction, respectively. The basic idea of the simulations is to cast stochastic trajectories for the adhesion cluster and average over many independent trials to obtain useful statistical information, e.g., the number of aggregated ICUs, the number of integrin–ligand bonds, etc.

In the simulations, the two kinds of reactions, i.e., integrin clustering and integrin–ligand bond binding, are solved alternatively, i.e., integrin clustering in the odd time steps and bond binding in the even time steps. In a specific single time step, we calculate the reaction time and identify the reaction position for the next reaction by using the Gillespie first-reaction method. That is, we generate a tentative reaction time for each reaction position by

$$\delta\tau_i^s = -\ln\xi_i^s / a_i^s. \tag{8}$$

where the superscript 's' indicates the type of reaction, i.e., $s=A$ for 'integrin clustering' and $s=B$ for 'integrin–ligand binding', and the subscript 'i' indicates the reaction position. ξ_i^s is the random number from the uniform distribution between 0 and 1, and a_i^s is the reaction rate of position i. The actual reaction time $\delta\tau^s$ for the next reaction is chosen as

$$\delta\tau_\mu^s = \min(d\tau_i^s). \tag{9}$$

where the position μ, corresponding to the smallest time step $\delta\tau_\mu^s$, is identified as the actual reaction position in the next time step.

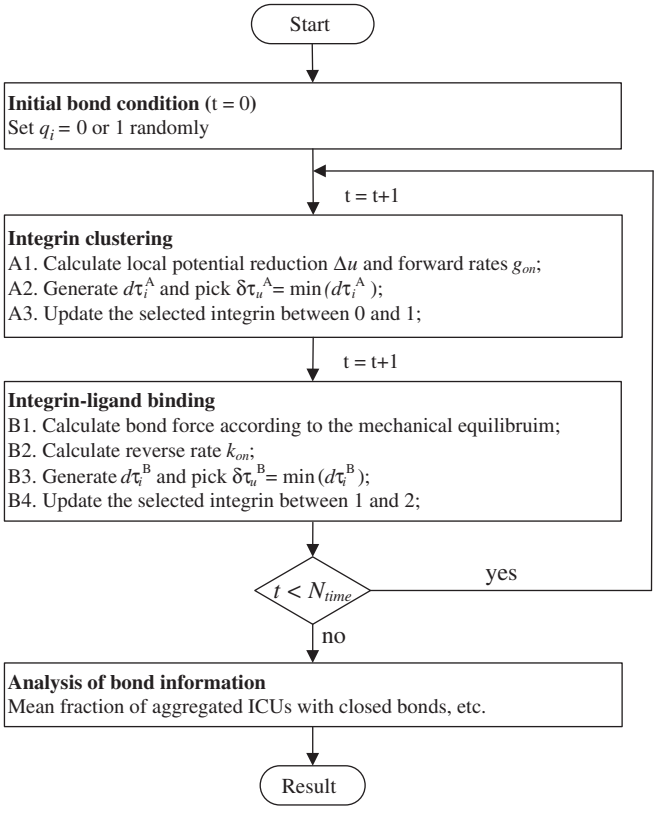

Fig. 2. The flow chart of numerical scheme of the Monte Carlo simulation on the responses of the FA to forces of different scales.

Table 1
The physiological ranges of the main parameters and their values chosen in the calculations.

Abbreviation	Definition	Physiological range	Used value	Source
l_0	Bond spacing		30 nm	(Arnold et al., 2004; Cavalcanti-Adam et al., 2006; Cavalcanti-Adam et al., 2007)
k	Bond stiffness	10^{-2}–10^{1} nN/μm	1 nN/μm	(Bell et al., 1984)
L	Bond length	10–100 nm	20 nm	(Bell et al., 1984; Ward et al., 1994)
k_{on}	Forward rate	1–100 s^{-1}	100 s^{-1}	(Lawrence and Springer, 1991; Rinko et al., 2004)
k^0_{off}	Reverse rate constant	1–10 s^{-1}	1 s^{-1}	(Bell, 1978; Rinko et al., 2004)
λ	Compliance length	0.01–1 nm	1 nm	(Erdmann and Schwarz, 2004a, 2004b; Krasik and Hammer, 2004)
g^0_{on}	Aggregation rate constant		1 s^{-1}	
g_{off}	Deaggregation rate		1 s^{-1}	

Then, to describe the reactions in the cluster, we introduce a state index q_i for ICUs, i.e., $q_i=0$ indicates a free ICU with opened integrin–ligand bond, $q_i=1$ indicates an aggregated ICU with opened integrin–ligand bond, and $q_i=2$ corresponds to an aggregated ICU with closed integrin–ligand bond. A free-opened ICU will become an aggregated-opened ICU after a forward reaction of clustering by changing state $q_i=0$ to 1, and vice versa, an aggregated-opened ICU will become a free-opened ICU via reverse reaction. Similarly, an aggregated-opened ICU will become an aggregated-closed ICU by changing state $q_i=1$ to 2 through the forward reaction of bond forming, and vice versa, an aggregated-closed ICU can become an aggregated-opened ICU via the reverse reaction.

For a clearer presentation, a scheme of our simulation algorithm is given in Fig. 2. At the initial time, there are N ICUs with $q_i=0$ or 1 generated randomly, denoting that there are only free or aggregated ICUs with open bond. In the odd time steps ($t=1, 3,\ldots$), we deal with the integrin clustering, and update the state of ICUs according to the Gillespie first-reaction method. And in the even time steps ($t=2, 4,\ldots$), we deal with the integrin–ligand binding dynamics, and update the state of ICUs according to the Gillespie algorithm (see Fig. 2). In the simulation, integrin clustering (A1–A3) and bond binding (B1–B4) were solved alternatively, until the time reaches the total step number N_{time} (10^4 steps in our calculations). The mean fraction of the aggregated ICUs with closed bonds Φ (the number of aggregated ICUs with closed integrin–ligand bond divided by the total number of integrins N) was obtained in each time step. The size of the FA is characterized by the mean fraction Φ. We have checked that the value of Φ always showed a plateau before the pre-set limit of simulation steps was reached. There are 200 integrin complex units (i.e., $N=200$) in our simulation (Table 1).

It is noteworthy that for the numerical convenience, we simulated the two kinds of reactions alternatively at odd and even steps. However, this choice of 'odd and even step' will not break the natural competition of the two reactions, because the reaction time of each reaction in the Monte Carlo simulation (see Eq. 8) is determined by its chemical reaction rate.

4. Results

Fig. 3 depicts the mean fraction of aggregated-closed ICUs (i.e., the size of FA) versus the traction force τ_{FA}. It shows that the FA only grows within a range of traction force. A force smaller than the first threshold value cannot induce FA growth because it cannot overcome the chemical potential barrier $\Delta\mu_0$ for aggregation (Nicolas et al., 2004). However, as soon as the traction force reaches the first threshold value, FA can grow due to the decrease of local chemical potential. It is noted that the first threshold value depends on the chemical potential barrier. The higher the barrier, the larger the threshold value for FA growth

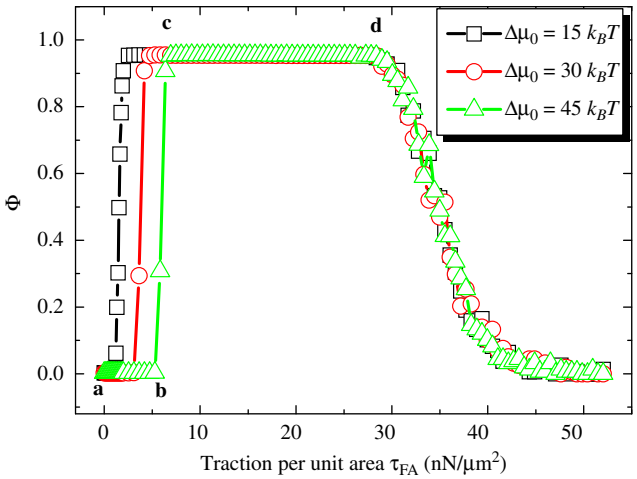

Fig. 3. The evolution of the mean fraction of aggregated-closed ICUs Φ (i.e., the size of the FA) with the increase of traction force at different $\Delta\mu_0$ values. Four regions are identified: (1) 'no-growth' region (a–b); (2) 'growth' region (b and c); (3) 'stable' region (c and d), and 'disassembly' region (d). In the simulations, we chose $N=200$, $k^0_{off}=1\ s^{-1}$, $k_{on}=100\ s^{-1}$, $g_{off}=1\ s^{-1}$, $g^0_{on}=1\ s^{-1}$, $l_0=30$ nm, $k=1$ nN/μm, $\lambda=1$ nm, and $k_BT=4\times10^{-12}$ J (Table 1).

(see Fig. 3). When the traction force is increased to a second threshold value, the focal adhesion begins to disassemble because the integrin–ligand bonds lose their stability under large traction force. Fig. 3 suggests four regions of the responses of FA to traction forces of different scales: (1) 'no-growth region'; (2) 'growth region'; (3) 'stable region'; and (4) 'disassembly region'.

The simulations show that in both 'no-growth region' and 'growth region', the integrin–ligand bonds are stable because the tension force in the bonds is small and the integrin–ligand bonds are insensitive to the traction force under relatively small force (Kong et al., 2008). Also, we found that in the growth region, the clustering of integrin complex units dominates the dynamic responses of the FA. In the 'stable region', while the growth rate of the FA is increasing, the disassociation rate of integrin–ligand bonds is increasing rapidly too, and the force induced aggregation and force induced disassembly are balanced. However, once the traction force τ_{FA} is increased beyond the second threshold value, majority of integrin–ligand bonds tends to break, and the binding dynamics of the integrin with ligand then dominates the response of FA. Therefore, the rupture of integrin–ligand bonds causes the shrinkage of the FA.

To further demonstrate that there are two threshold values, respectively, for the growth and the disassembly of FAs, we introduce a thermodynamic model to calculate the flux of ICUs (see Supplementary materials S3). Fig. 4 depicts the flux of ICUs versus the traction force. The comparison between our results and that of Shemesh et al. (2005) is also made. Our predictions clearly

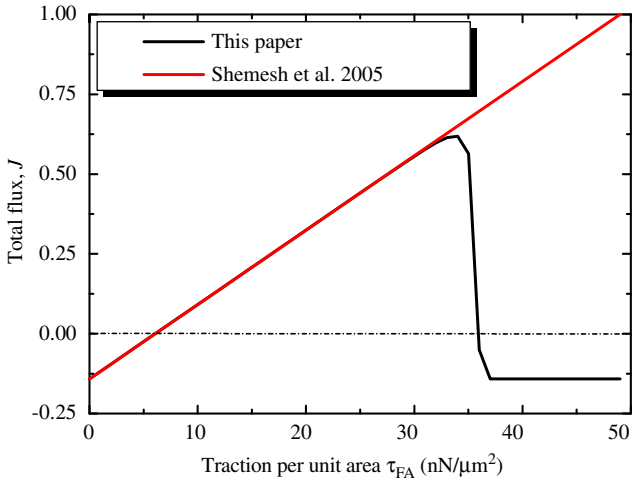

Fig 4. The prediction of the growth behaviors of the FA by the thermodynamic model of this paper in comparison with that of Shemesh et al. (2005). In the calculations, we chose $W=15\ k_BT$, $k=1$ nN/μm, $\Delta\mu_0=40\ k_BT$, and $l_0=30$ nm.

show that there exists an 'optimal' region of traction force for the growth and stability of FA, within which the FA can grow and integrin–ligand bonds are stable as well. However, the force lower than the first critical force value will cause the shrinkage of the FA while that higher than the second critical value will induce disassembling the FA. These results again show that the responses of FA to different scales of mechanical force are determined by the interplay of the two reactions, i.e., the integrin aggregation and integrin–ligand binding. In contrast, Shemesh et al. (2005) predicted an unlimited growth because they did not consider the integrin–ligand binding dynamics in their model.

5. Discussions

Force-induced growth and force-induced instability are both typical responses of cell adhesion which are seemingly very contradictory. In this study, a microscopic model was proposed for studying the different responses of the FA by treating it as an adhesion cluster. In the microscopic model, we introduced two generic molecular mechanisms, i.e., integrin clustering and integrin–ligand binding dynamics, which depend on the applied force. Two different kinds of chemical reactions were used to describe the integrin clustering and integrin–ligand binding dynamics. The two chemical reactions in the cluster were solved by using Monte Carlo simulation with Gillespie method. The evolution of the FA size was analyzed for studying the effect of traction force on the responses (growth or disassembly) of the FA. The simulation results showed that there are two critical force values that define different FA dynamics. The force-induced FA growth happens at relative small force scale, which is dominated by the clustering dynamics of integrin complex units. In contrast, the force-induced disassembly of FA, such as cell reorientation, happens at relative large force scale, which is dominated by the integrin–ligand binding dynamics. Its strict dependence on forces of different scales is one of the intriguing features of mechanosensitivity of focal adhesions.

We showed that the predictions of the microscopic model broadly agree with the experiments not only qualitatively but also quantitatively. We predicted that there is no growth when the force is smaller than the first critical value, but the FA starts to grow when the force is increased to be higher than this first critical value. This prediction on FA growth is consistent with the theoretical studies of Safran with coworkers (Nicolas et al., 2004) and Shemesh et al. (2005). Our simulations showed that the first critical force is about 5 nN/μm^2. The experimental evidence for this threshold value is that there is a linear relationship between the force and the area of FAs. The constant relating force and FA area is found to be 5.5 ± 2 nN/mm^2, i.e., the average stress on focal adhesion that can induce the growth of focal adhesion is around 5 nN/μm^2 (Balaban et al., 2001; Bershadsky et al., 2003; Riveline et al., 2001; Tan et al., 2003; Zaidel-Bar et al., 2003).

Furthermore, when the traction force is increased to be higher than the second critical value, around 40 nN/μm^2, the FA starts to disassemble. This prediction is consistent with the experiments in which when the cell is stretched by the cyclic stretching, the cells will reorientate themselves when the stretching strain is higher than 5% (Neidlinger-Wilke et al., 2001). By using a cluster model, and considering the stiffness of stress fiber and adhesion bonds, the traction force corresponding to the 5% stretching amplitude is estimated to be 48 nN/μm^2 (Kong et al., 2008), which is consistent with our microscopic model. We showed that the traction force that induces the disassembly of FAs is much higher than that induces the growth. In addition, this work showed that developing the microscopic model might be an effective approach to consider many different mechanisms in a unified theoretical frame for studying complex behaviors of cell adhesion, such as mechanosensitivity of FAs. It is noteworthy that the dynamics of actin filaments (especially the stress fiber, the bundle of the actin filaments) may also play important roles in cell adhesion (Geiger et al., 2009; Gerthoffer and Gunst, 2001; Riveline et al., 2001; Sastry and Burridge, 2000). However, according to the mechanical measurement, the breaking force for a stress fiber is on average 377 nN (Deguchi et al., 2006), which is much larger than the rupture force of a focal adhesion, which is on the order of tens of nN (Kong et al., 2008; Mack et al., 2004). Therefore, the cell reorientation under the cyclic loading is more likely caused by the rupture of FAs.

Our predictions on the instability of FAs not only can be applied to the cells under simple and uniaxial stretching but also can be applied to that under equi-biaxial stretching. Since the deformation of the substrate is uniform along all the direction under the equi-biaxial stretching, the cell should seek other ways to avoid the extra-large deformation instead of reorientation. A direct verification for this prediction might be the experiments by Wang et al. (2001) on the endothelial cell under equi-biaxial stretching. In response to equi-biaxial stretching (10% 1 Hz), the actin cytoskeleton of the endothelial cell was remodeled into a 'tent-like' structure oriented out of the membrane plane in only 15 min to avoid the cyclic stretching.

Conflict of interest

The authors state that they have no any financial, professional, and personal conflict of interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jbiomech.2010.05.019.

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