细胞粘附力敏感性的微观力学模型 *

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Focal adhesions (FAs) are large, multiprotein complexs that provides linkers between cytoskeleton to the extracellular matrix (ECM). Cells sense and respond to forces through FAs to regulate a broad range of processes, such as cell growth, migration, differentiation and apoptosis. Currently, the underlying mechanisms of the force dependent mechanical properties/features of FAs have not yet fully understood. For example, strong mechanical forces (including those developed in some cases by cells themselves) can, obviously, disrupt cell–cell and cell–matrix adhesions. However, recent experiments also demonstrated the existence of force dependent adhesion growth (rather than dissociation). These surprising results stimulated biologists, chemists and physicists to study this intriguing phenomenon extensively, and to attempt to model it theoretically.

In this talk, a microscopic model of the FA is proposed for understanding the different responses of cell to forces of different scales (see Fig. 1), in which the FA is modeled by a molecular cluster. Two microscopic features of FAs are considered: ‘integrin-integrin’ assembly dynamics and ‘integrin-ligand’ binding dynamic. That is, the integrin proteins can not only assemble to or dissemble from the adhesion plaque, but also can bind with or detached from the ligand on extracellular matrix. We assumed that the integrin-integrin assembly is driven by the local chemical energy reduction characterized by forward rate g_{on} and reverse rate g_{off}; and the integrin-ligand binding dynamics is determined by the tension in adhesion bond due to the external force, characterized by forward rate k_{on} and reverse rate k_{off}.

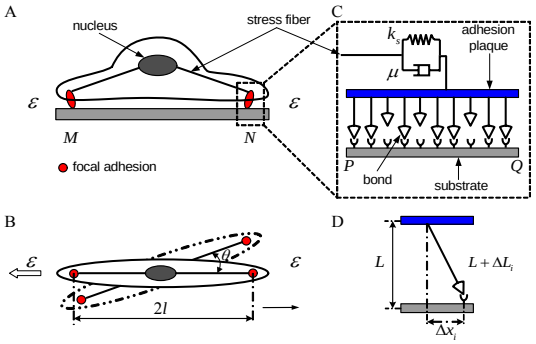

Figure 1. The microscopic model of the focal adhesion

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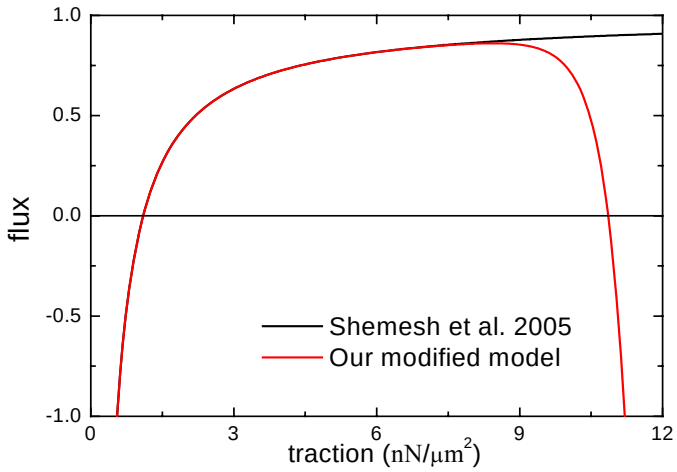

Figure 2. The growth rate of the FA versus the traction force

The dynamics of the coupled integrin-integrin and integrin-ligand interactions of the adhesion cluster is solved by Gillespie algorithm. The basic idea of such Monte Carlo simulations is to cast stochastic trajectories for the adhesion cluster and average over many independent trials to obtain useful statistical information. We show that there exist three force scales corresponding to different dynamic states of FAs. When the force is small, there is no growth of FAs. As soon as the force is increased up to a critical value around 5.5nN/um^2, it then induces FA growth because the integrin-integrin dynamics dominates the dynamics of FAs and the applied force leads to recruitment of integrins to the adhesion plaque. When the force is increased to a scale up to an intermediate level region, the integrin-integrin dynamics and integrin-ligand dynamics are balanced, and therefore the adhesion cluster is stable, i.e., no net growth in FAs. However, when the external force is increased to a second critical force level, the force will induce the disassembly of FAs due to the rupture of integrin-ligand bonds, as the bond rupture dominates the dynamics of the FAs.

In this study, a unified microscopic model that can take into account the molecular mechanisms of focal adhesion is developed. We showed that it can predict not only the cell reorientation (disrupt of FA) but also the force induced growth at different force scales within one theoretical frame. The essence of this work is that it connects the dynamics of the adhesion bonds (molecular level) with the cell's behavior (macroscopic level) through the mechanics of stress fiber and deformation of adhesion plaque. The predictions of this model are consistent with experimental observations.

References

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