PROBING MECHANICAL PRINCIPLES OF CELL-MATRIX FOCAL ADHESION: A COUPLED STOCHASTIC-ELASTIC FRAMEWORK

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Summary Unlike adhesion of conventional hard materials in engineering commonly described by JKR and DMT type models, the exact nature and mechanism of adhesion between soft cells and extracellular matrices (ECM) are far from understood. Cells are known to probe and feel the mechanical property of their surrounding microenvironment, and respond to the presence of cytoskeletal and/or external stresses via localized focal adhesions. We will present some recent theoretical and numerical studies aimed at probing the basic mechanical principles of focal contacts in cell-matrix adhesion via stochastic-elasticity models. The field distributions of interfacial traction and deformation are assumed to obey classical elasticity descriptions whereas the rupture and rebinding of individual molecular bonds are governed by stochastic equations. Results and discussions will be organized to address the key experimental observations on focal adhesion, which present strong size effect, stiffness dependence and force regulation.

INTRODUCTION AND MODEL

Cell adhesion plays a central role in many biological functions including cell migration, spreading, differentiation and growth. A capability to control cells' interaction with their environment, for which a quantitative description of cell adhesion is a critical step, will be essential for tissue and cellular engineering, and has the long-term potential of providing scientific guidance for revolutionizing biology and medicine. A number of recent developments on cells' responses to their mechanical environment highlight the importance of mechanics research in this field: Cells cultured on rigid glass or plastic dishes typically develop discrete micron-sized sites of cell–matrix adhesion, i.e. focal contacts in which cytoskeletal actin bundles are anchored [1]; It has been found that focal adhesions are gradually decreased as cells are cultured on increasingly more compliant substrates for fibroblasts and endothelial cells [2], and cells cultured on elastically nonhomogeneous substrates can actively migrate towards stiffer region, a phenomena known as durotaxis [3]; Cell growth and differentiation can be solely controlled by the stiffness of the underlying substrate [4]. All these tightly regulated processes involve sensing mechanical property of cell's environment in a magnitude-sensitive manner and may share a similar mechanosensory mechanism. We consider an idealized theoretical model of a cluster of molecular bonds between two dissimilar elastic media subjected to an applied tensile load, aiming to provide possible explanations for a wide range of experimental observations and suggest multiple mechanisms by which cells can actively control adhesion and deadhesion via cytoskeletal contractile machinery in response to mechanical property of their surroundings.

Stochastic descriptions of bond dissociation and association

Cell-matrix adhesion depends on the collective behavior of specific receptor-ligand bond clusters and the dissociation and association of single molecular bonds are assumed to be governed by stochastic descriptions. The process of bond dissociation is often regarded as thermally assisted escape over a potential energy barrier. Application of a mechanical force changes the energy landscape and therefore influences the rupture process. The seminal model of Bell [5] gives that the bond dissociation rate $k_{\text{off}} \sim \exp(F)$, where F is the force acting on the bond. Single molecular bonds are unstable of the order 1-100 seconds even without an applied force.

The long-term stability of a multiple-bond adhesion, such as those in cell-matrix focal adhesions, is attributed to the cooperative effects that individual bonds can rebind after they break until the whole adhesion ensemble is failed. Rebinding of an open bond can occur as long as the broken receptor and ligand pairs are held in proximity for sufficient amount of time. In modeling bond association, the whole process is regarded as consisting of two steps [6]: the receptor and complementary ligand first have to come sufficiently close in space to form a complex; second, the complex reacts at an intrinsic time scale to complete the final receptor-ligand bonding. Approximately, the rebinding rate is inversely proportional to $\exp(\delta^2)$, where δ is the separation distance between the two opposing surfaces with functional molecular pairs. This strongly decaying behavior of rebinding rate with increasing separation is expected to play a very important role in the dynamics and stability of molecular bond clusters in the presence of cell-matrix deformability. Once the opposing surfaces are separated locally at open bonds by more than a critical distance, bond rebinding becomes hardly possible and the adhesion cluster is expected to undergo a catastrophic failure process.

Elastic Green's function approach for interfacial adhesion of multiple bonds

The analytical solution to the interfacial adhesion of multiple bonds is generally unavailable in the case of compliance-induced spatially dependent rupture and rebinding rates. The elastic descriptions of interfacial force and surface separation between cell and extracellular matrix can be incorporated into the stochastic dynamics of bond clusters

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through an elastic Green's function approach for various settings [7-9]. A two-scale Monte Carlo scheme has been developed based on Gillespie's algorithm [10] to numerically solve the spatiotemporal process governed by the cluster evolution dynamics. Stochastic trajectories are cast in accordance with the above described reaction rates and then many independent trials are averaged to obtain useful statistical information. In our simulations, each bond location is considered an independent reaction site, and the reaction rates, either dissociation or association, are determined from the computed forces on closed bonds and surface separations at open bonds. The "first reaction method" of Gillespie's algorithm is used to determine when and where the next reaction will occur through random number sampling. When the binding state of any bond (open versus closed) has undergone a change, an update of the force and surface separation at all bonds is performed using the associated elastic Green's function, and the results are used to determine the subsequent bond events. This coupling between elasticity modeling of interfacial traction/separation and stochastic events starts at the initial state when all bonds are closed and the process proceeds until all bonds within the adhesion domain become open. The total elapsed time is recorded as the adhesion lifetime, a direct measure of cluster stability.

RESULTS AND CONCLUSIONS

Our theoretical modeling framework and coupled numerical simulations have revealed the following principles on the mechanics of focal contacts in cell-matrix adhesion:

(i) Size effect - principle of enhancing adhesion by bond clustering [7,8]: Compared to isolated receptor-ligand bonds, clustering of multiple bonds into focal contacts greatly enhances the lifetime and stability of cell-matrix adhesion.

(ii) Stiffness dependence - principle of enhancing adhesion by increasing the reduced elastic modulus of cell and matrix: Small modulus, which could result from the presence of a soft matrix or dissolution of cytoskeleton, has two devastating effects on focal contacts. First, it induces severe stress concentration near the adhesion edges and crack-like failure around the contact rims, which places an upper limit on the size of focal contacts [7,8]. Second, small modulus tends to increase local surface separation at open bonds and make them difficult to reform the adhesion, effectively killing the possibility of bond rebinding [9].

(iii) Regulation by force direction [8]: The adhesion lifetime depends sensitively on the direction of stress fibers that exert pulling forces on the focal contacts. For a given magnitude of pulling force, there usually exists a critical angle at which the adhesion lifetime rapidly rises to long-term stability.

(iv) Regulation by cytoskeletal pretension [11]: Cytoskeletal pretension induced by myosin contractility tends to smooth out the distribution of forces on receptor-ligand bonds between individual stress fibers and matrix, thereby increasing adhesion lifetime by orders of magnitude. This important effect of cytoskeleton contractility may provide a very effective control for cells to regulate adhesion with extracellular matrix through metabolic activities in the cytoskeleton.

Our stochastic-elastic modeling framework has been built upon the classical model of Bell and its recent extensions, and been used to address the intriguing mechanics-related questions raised by experiments on cell-matrix focal adhesion. While the predictions from this model are consistent with most of the findings that focal adhesions alter their behaviors as a result of changes in cluster size, cell/matrix rigidity and cytoskeletal contractility, we caution that some of the assumptions made have not been experimentally proven and should be further investigated.

More generally, such an approach can be extended to a broad range of more complicated situations in cell adhesion involving spatially dependent ECM deformability, non-uniform traction boundary, multiple types of molecular bonds, and/or nonhomogeous bond density.

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