主题发言

Mechano – Chemical Coupling at Molecular Level: Forced Dissociation of Selectin/Ligand Binding

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Mechano – chemical coupling is a common phenomenon that exists in various biological processes at different physiological levels. Bone tissue remodeling strongly depends on the local mechanical load. Leukocytes are sheared to form the transient aggregates with platelets or other leukocytes in the circulation. Flow pattern affects the signal transduction pathways in endothelial cells. Receptor/ligand interactions are important to cell adhesion since they supply the physical linkages among cells. How external forces influence the biological function has little been known, and nowadays attract more and more attentions. Here the forced dissociation of selectin/ligand binding is used to test mechano – chemical coupling at molecular level.

To conduct such a test, a dual approach is taken that coordinates biological experiments, mechanical measurements, and numerical computation of cell adhesions and molecule binding. The approach comes from three aspects: (1) A theoretical framework was established upon a small system probabilistic model firstly proposed by McQuarrie[1,2] and then modified by other workers[3-6]. Coupled by the constitutive equation of force dependence of reverse rate[7,8], this framework was employed to predict the kinetics of selectin – mediated cell adhesions under external forces. (2) The state – of – the – art technologies developed includes micropipette aspiration, atomic force microscopy (AFM), dual optical trap, and quantitative rosette assay. Combined with the relevant assays in cellular/molecular biology and immunology, these techniques enable to measure experimentally the force dependence of selectin/ligand dissociation. (3) A numerical simulation of steered molecule dynamics, based upon a non – equilibrium physical theory from a viewpoint of atomic level, is used to predict the energy landscape of forced dissociation of selecin/ligand interactions.

Biological issues focus on the structure – functionality of selectin/ligand interactions under external forces. Here we concentrate on the effects of molecular length, orientation, and surface microtopology, the effects of amino acid mutation of selectins and their ligands, and the dependence of force spectrum and energy landscape on approaching rate, dislodging velocity, and contact force. Molecular systems mainly consist of a family of selectins, important adhesive molecules to inflammatory response and tumor metastasis, and their ligands (*e. g.*, P – selectin glycoprotein ligand 1)[9,10]. While one molecule was coated or captured on one cell/sphere surface or an AFM tip, the counterpart molecule was immobilized onto the other cell/sphere surface or a reconstructed lipid bilayer. Using various laboratory techniques as above, the adhesion probability of, the rupture force distribution of, and the force dependence of bond lifetime of selectin/ligand interactions were measured experimentally. Kinetic parameters of reaction rates and binding affinities were obtained by comparing the data to the probabilistic model, while force dependence of selectin/ligand dissociation were predicted using the first – order kinetics of bond dissociation. Experimental data and theoretical predictions showed that the selectin/ligand interactions were significantly influenced by external force, which in turn affected the biological functions of biomolecules[3-6,11]. These findings further the understandings of mechano – chemical coupling in cell adhesion mediated by adhesive molecules. (Supported by NSFC grants 10072071, 10128205, and 30225027, a TRAPOYT award and NIH FICRA grant 1 R03 TW05774 – 01).

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