Cellular and Molecular Biomechanics Laboratory (Zhu Lab)

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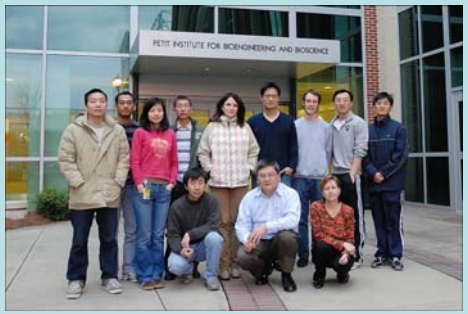
Georgia Institute of Technology, Atlanta, GA, USA

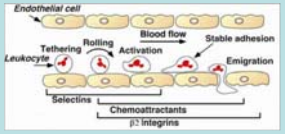


INTRODUCTION

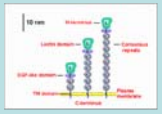
Our interests are focused on adhesion and signaling molecules involved in processes of inflammation, hemostasis, and T-cell activation. We use various combined experimental, computational, and theoretical methods to study the mechanics and kinetics of cell and molecular interactions at the level of single pair of cells and single pair/triad/group of molecules. Our research provides knowledge to understand mechanisms associated with inflammatory reaction, bleeding and thrombotic disorders, immuno-deficiencies, autoimmune diseases, cardiovascular diseases, and cancer.

Current projects includes studies of selectins and ligands, integrins and ligands, plalete glycoprotein Ib (GPIb), von Willebrand factor (VWF), and ADAMTS-13, and T cell receptor (TCR) and associated molecules.

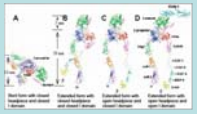
I. Adhesion cascade of inflammatory reaction



II. Selectins and Integrins

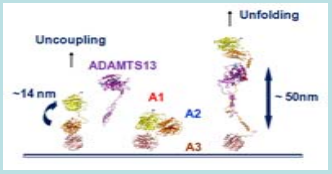


(a) Selectin

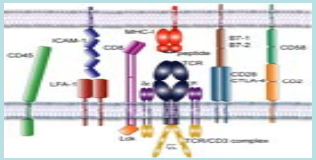


(b) Integrin

III. VWF cleavage by ADAMTS13



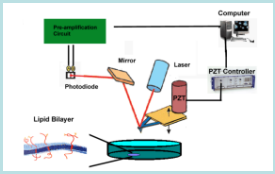
IV. T cell receptor and associated molecules



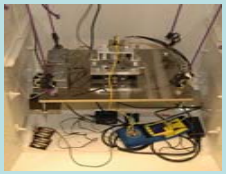
EXPERIMENT AND ANALYSIS

A. Atomic Force Microscopy (AFM)

AFM is used to study mechanical regulation of molecular interactions, conformational changes, and proteolysis. Using AFM, we demonstrated catch bonds selectin/ligand, GPIb/VWF, and integrin/ligand interactions. Catch bonds are counter-intuitive behaviors where force prolongs lifetimes of molecular bonds, which is oppsite to the ordinary behavior of slip bonds where force shortens lifetimes.



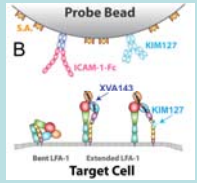
(a) Schematic of AFM Experiment



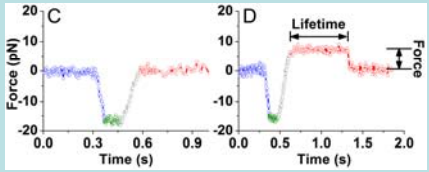
(b) Home-made AFM setup

B. Biomembrane Force Probe (BFP)

BFP uses a red blood cell as a force transducer, which can provide a much softer spring (0.3 pN/nm) to probe single molecule interactions with higher force resolution (~1 pN).



(A) Photomicrograph of BFP
(B) Schematic of an experimental setup



Force scan curves showing the absence (C) or presence (D) of adhesion and lifetime measurement at a constant force.

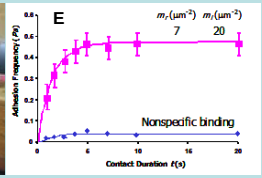
C. Micropipette Experiment

Micropipette-aspirated red cell is utilized to detect adhesion events and measure adhesion probability. The 2D binding kinetics and affinity of the specific molecular interaction are determined by comparing data to a probabilistic kinetics model:

$$P_a = 1 - \exp\{-m_r m_l A_c K_a (1 - \exp(-k_{off} t))\}$$

(A) Impingement (B) No binding (C) Detect binding

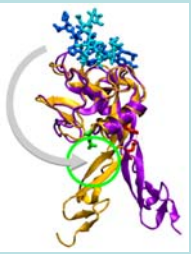
(D) Micropipette setup

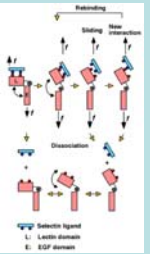


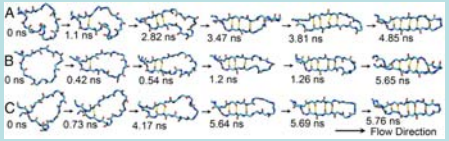
(E) Adhesion frequency vs. contact time

D. Molecular Dynamics Simulations

Molecular dynamics (MD) are used to simulate receptor-ligand interactions and to induce conformational changes. Simulations provide insights to structure-based molecular mechanisms.



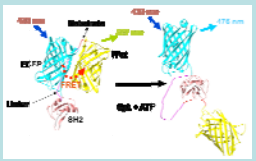


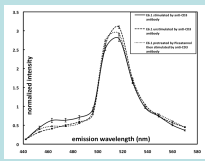


Simulated structures of flow-induced conformational changes in wild-type (A), gain-of-function (B), and loss-of-function GPIbα β-switch

E. Fluorescent Biosensor

Biosensors are used to visualize activities of kinase molecules following cell receptor engagement that triggers signaling.





Syk kinase activity reported by biosensor fluorescent activity in the open and closed conformation

For more information, please visit out website :
http://www.bme.gatech.edu/groups/zhu