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Control of ligand-receptor interaction by tuning the molecular environment

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Cell adhesion is a fundamental biological process mediated by specific molecular bonds between ligands and receptors attached to surfaces. The formation and rupture of these bonds depend on the kinetic and mechanical factors (distance between binding partners, force applied on bond, diffusion of molecules) and, as it has been recently observed, on the topography of the surfaces.

The goal of our work is to quantify the effect of these parameters starting with antigen/antibody as a model system (chosen antigen is the ICAM1) and measuring the binding and unbinding kinetics using the laminar flow chamber technique. We observe how the ligand-receptor interaction can be modified by tuning the molecular environment, playing i) on the topography of the surface, using glass slide with different roughness, ii) on the multivalency of the molecules involved in the bond formation, iii) on the mobility of the surface, comparing an immobile system with a mobile one using fluid supported lipid bilayers (SLB).

It has been already shown that adhesion receptors are influenced by the surface topography, although the results are still controversial. We performed adhesion experiments in *laminar flow chamber* varying the roughness (from 50nm to 700nm) of the substrate where investigated molecules are attached. A systematic comparison between them didn't show differences either in the adhesion frequency or in the detachment of the ligand-receptor bonds. To interpret these results we build a model taking into account the actual contact areas, analysing directly AFM images of the samples.

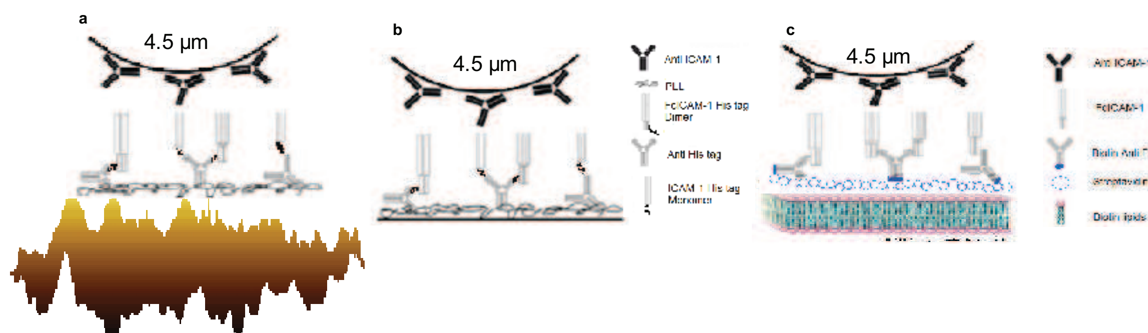

Fig. 1*: Laminar flow chamber experiment in which a receptor coated beads is driven on a ligand coated substrate by a hydrodynamic flow.* ***a****: ligand coated rough substrate.* ***b****:smooth substrate coated with monomer and dimer ICAM-1.* ***c****: investigated ligand on fluid supported lipid bilayer.*

We are also working on the multivalency aspect studying monomeric and dimeric ICAM1 in the adhesion, knowing that *in vivo* adhesion receptors often present a dimerized structure. At low shear rate, corresponding to low applied force, mICAM1 and diICAM1 present a similar bond lifetime and adhesion frequency. While bond lifetime is independent on the applied force for diICAM1, it is shortened by applied force for mICAM1. Additionally, the adhesion frequency decreases faster for mICAM1 with applied shear rate. We intend to interpret this behaviour in terms of time reinforcement of the diICAM1-anti ICAM1 bond.

Recent results in the laboratory show that the binding efficiency scales non linearly with the encounter duration [1]; in other words, there is a minimal time τ_0~10 ms required to form the bond. To test this prediction, we put ligands on SLB to investigate how the diffusion (coefficient D) can modify the adhesion through the relation $\tau \sim L^2/D$. First results don't show a reduction of adhesion on fluid bilayers which may be either due to insufficient ligand diffusion or formation of multiple bonds

Références

[1] P. Robert et al., “Biomolecule association rates do not provide a complete description of bond formation”, Biophys. J. volume 96, pp. 1-9 (2009).

Je souhaite concourir au prix « présentation orale » et je déclare être une chercheuse non-permanent n’ayant pas encore soutenu la thèse.