Cell adhesion via antibodies or immunoadhesins to surfaces displaying Fc receptors

Ryan N. Gutenkunst[1], Daniel Coombs[2], Toby Starr[3], Michael L. Dustin[3], and Byron Goldstein[3]

***Short Abstract* — We quantitatively study the adhesion, mediated by antibodies or immunoadhesive molecules, of cells to surfaces displaying antibody-binding Fc receptors. We extend a previous model [1] by incorporating heterogeneity in target cell epitope density and epitope immobility. We analyze experiments on the adhesion of Jurkat T cells to bilayers containing the receptor FcγRIIIB, with adhesion mediated by the drug alefacept. We show that a model in which all target cell epitopes are mobile and available for binding is inconsistent with the data, suggesting more complex mechanisms are at work. We hypothesize that the immobile epitope fraction may change with cell adhesion, and we show that this model is more consistent with the data. We also quantitatively describe the parameter space in which binding occurs, offering guidance for drug design. Our results point toward mechanisms relating epitope immobility and cell adhesion, and they offer insight into the activity of an important class of drugs.**

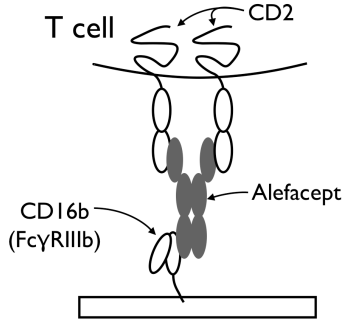
I. Introduction

A promising direction in drug development is the exploitation of antibody-dependent cell-mediated cytotoxicity, in which a target cell labeled with antibodies is killed upon adhesion to a natural killer cell [2]. Drugs designed to exploit this process typically bind cell-surface epitopes that are overexpressed on target cells but that are also expressed on other cells. Thus it is important to understand the factors governing adhesion of cells by antibodies and similar molecules.

To develop a quantitative understanding, experiments were carried out which mimic such adhesion [1]. Jurkat T cells were allowed to adhere to bilayer surfaces containing the receptor FcγRIIIB. This adhesion was mediated by the drug alefacept, an antibody-like fusion protein. The tail of alefacept binds FcγRIIIB and the two arms bind CD2, a natural receptor on T cells. By imagine from below, these experiments measured, as a function of alefacept concentration, the fraction of T cells adhered, the average contact area, and the number of bridging FcγRIIIB-alefacept-CD2 bonds.

II. Modeling

We begin by considering the simplest equilibrium model for adhesion, in which both the CD2 epitopes on the T cell and the receptors on the bilayer are freely diffusing. We model the distribution of CD2 eptiope density among T cells by a two-parameter Weibull distribution. Fitting this model to the data, we find that it dramatically underestimates the amount of CD2 on the T cells as assayed by FACS.



One potential reason for the simple model to underestimate CD2 density is that in actuality not all CD2 epitopes are freely diffusing. Experiments on unstimulated T cells find that 13% of CD2 are immobile [1], and this immobile fraction can change with stimulation [3]. We thus introduce an immobile population of CD2 and refit the model. Surprisingly, we find that if the immobile fraction is taken as a fit constant, the optimal immobile fraction is 0. This motivates us to consider more complex models, in which the immobile fraction changes with cell stimulation. We find that a model in which the immobile fraction is a linear function of the contact area better fits the adhesion data and substantially improves agreement between our estimated CD2 density and the experimental value.

Using our model, we further demonstrate that we can accurately predict the degree to which nonspecific IgG inhibits adhesion. We also derive analytic expressions for the smallest and largest drug concentrations that will drive adhesion.

[1]Theoretical Biology and Biophysics & Center for Nonlinear Studies, Los Alamos National Laboratory. E-mail: ryan@gutenkunst.org
[2]Mathematics, University of British Columbia
[3]Pathology, New York University School of Medicine and Molecular Pathogenesis, Skirball Institute of Biomolecular Medicine
[4]Theoretical Biology and Biophysics, Los Alamos National Laboratory

References

[1] Dustin ML, et al. (2007) *J Biol Chem* **282**, 34748.
[2] Iannelo A, Ahmad A (2005) *Cancer Metastasis Rev* **24**, 487.
[3] Zhu DM, et al. (2006) *ACS Chem Biol* **1**, 649.