

Antigen Recognition at Immune-Cell Interfaces: Probing the Role of Mechanical Forces

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Short Abstract — One of the central problems in immunology involves molecular recognition at cell-cell interfaces. Fascinating recent experiments have revealed that mechanical forces regulate processes by which T cells and B cells identify molecular signatures of pathogens. In this work, we develop hybrid computational models that account for key biophysical properties of immune cell interfaces, including stochastic receptor-ligand binding kinetics, membrane mechanics, and actin-mediated forces on the membrane. We use these models to investigate how mechanical forces modulate the interactions of T cells and B cells with surface-presented antigens.

I. INTRODUCTION

UNDERSTANDING mechanical forces and dynamics at membranes is critical for understanding how T cells and B cells distinguish between self and foreign ligands, and how they subsequently respond to antigens [1]. Both cell types use surface receptors to identify molecular signatures of pathogens. Because T cells and B cells physically engage other cells in direct contact, they are subject to a variety of mechanical forces. For example, their surface receptors experience forces due to membrane deformations, cell motion, and coupling to the dynamic actin cytoskeleton. Mechanical forces play important roles in the regulation of immune cell activation [1,2], and new experimental probes are beginning to provide details about forces at cell-cell interfaces [3].

II. RESULTS

In this work, we use computational and theoretical methods to investigate the role of mechanical forces at T cell and B cell surfaces. Our methods combine a continuum description of membranes with stochastic reaction-diffusion kinetics of surface receptors [4,5]. We use the methods to study two related problems.

A. T cells: Force-dependent dissociation kinetics

T cells use the T cell receptor (TCR) to identify peptide fragments presented by surface molecules (pMHC) on other cells. Experiments have shown that stimulatory TCR-pMHC bonds behave as catch bonds [2], with an average bond lifetime that initially increases with an increasing tensile force. Because T cells are initially stimulated by small numbers of TCR-pMHC complexes, it is important to

understand how bond formation drives dynamic changes in membrane organization and shape, how these changes affect forces experienced by the bonds, and how these forces affect bond lifetimes.

We characterize time-dependent forces on TCR-pMHC bonds in response to dynamic membrane changes [4]. We then determine the distributions of bond lifetimes using force-dependent lifetime data for TCRs bound to various ligands. Strong agonists, which exhibit catch bond behavior, are markedly more likely to remain intact than antagonists. Thermal fluctuations of the membrane shape enhance the decay of the average force on a bond, but also lead to fluctuations of the force. When more than one bond is present, the bonds experience reduced average forces, leading to changes in lifetimes.

B. B cells: Membrane-dependent affinity threshold

The activation of B cells is controlled largely by the B cell antigen receptor (BCR). Although B cells can be activated by soluble antigens, B cells *in vivo* are activated predominantly by antigen attached to membrane surfaces. Experiments have revealed that B cells use mechanical forces transmitted by the actin cytoskeleton to discriminate between antigens of similar binding affinity and to internalize portions of the antigen-presenting surface [6].

We study dynamics of BCRs at an intermembrane junction and show that the bending rigidity of the antigen-presenting membrane influences the affinity at which antigens are internalized through a mechanism involving BCR clustering. The clustering and membrane invagination occur with marked stochasticity near the affinity threshold.

Taken together, our results highlight the importance of forces at immune-cell interfaces, and we conclude by discussing our results in the context of antigen discrimination by T cells and B cells.

REFERENCES

- [1] Depoil D, Dustin ML (2014) Force and affinity in ligand discrimination by the TCR. *Trends Immunol* **35**, 597-603.
- [2] Liu BY, Chen W, Evavold BD, Zhu C (2014) Accumulation of dynamic catch bonds between TCR and agonist peptide-MHC triggers T cell signaling. *Cell* **157**, 357-368.
- [3] Liu Y, et al. (2016) DNA-based nanoparticle tension sensors reveal that T-cell receptors transmit defined pN forces to their antigens for enhanced fidelity. *Proc Natl Acad Sci USA* **113**, 5610-5615.
- [4] Pullen RH, Abel SM (2017) Catch bonds at T cell interfaces: Impact of surface reorganization and membrane fluctuations. *Biophys J* **113**, 120-131.
- [5] Li B, Abel SM (2018) Shaping membrane vesicles by adsorption of a semiflexible polymer. *Soft Matter* **14**, 185-193.
- [6] Spillane KM, Tolar P (2017) B cell antigen extraction is regulated by physical properties of antigen-presenting cells. *J Cell Biol* **216**, 217-230.

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