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IDEA TO WATCH

Thoughts & Opinion

Naturally evolvable antibody affinity may be physically limited

Naturally evolving antibodies attain elevated affinity in germinal centers (GCs).[1] In these dynamic open micro-structures, competition between B cell clones and their somatic mutants drives an increase in average affinity across individual populations of up to a few thousand cells. Such evolutionary learning of the antigenic target (known as affinity maturation), however, eventually saturates. Most notably, the saturation affinity is orders of magnitude lower than what is realizable in vitro via directed evolution. What exactly halts in vivo evolution and sets the affinity ceiling remains an outstanding puzzle in immunology.

Three decades after Eisen and Siskind discovered affinity maturation in 1964, Foote and Eisen[2] put forth the key insight that constraints extrinsic to antibody-antigen interaction may exist and limit affinity maturation. This recognition suggests an origin of the ceiling compatible with the lack of improvement despite a persistent heterogeneity in antibody affinities: Considering soluble antigen, Foote and Eisen estimated the ceiling from an upper bound of the on rate conferred by diffusion and a lower bound of the off rate set by antigen internalization by B cells.[2] This estimate is very close to the observed ceiling, and the rationale was validated by Batista and Neuberger.[3] Yet, it has become clear that membrane-bound, rather than soluble, antigens are most important for B-cell activation in vivo.

In this issue, Desikan *et al*.,[4]make a conceptual step forward by extending the original insight to antigen tethered to the surface of follicular dendritic cells (FDCs) in GCs, a modern view uncovered by intravital imaging technology. Importantly, GC B cells exert mechanical pulling forces generated by the actin cytoskeleton on the B cell receptor (BCR), rupturing the membrane-tether in order to acquire the antigen.[5] The authors hypothesize that the affinity ceiling stems from physical limits to the strength of the chain of protein complexes linking GC B cells to FDCs for antigen acquisition. Further, the weakest link in the chain sets the limit.

Using known equilibrium binding free energies of the links involved, Desikan *et al*., estimate the saturation affinity by considering a single antigen extraction event. A further step was taken to consider possible configurations of multivalent antigen presentation. The central idea is that the ceiling is reached once the affinity of the presenting antibody for the antigen (in the form of immune complexes attached to the FDC) exceeds the overall strength of the antibody-FDC tether. A key premise underlying the idea is antibody feedback; it was observed that antibodies can return to GCs and replace current antigen-presenting antibodies, if the former had a higher affinity for the antigen.

This study of Desikan *et al*., highlights the value of considering the physical process of antigen extraction, drawing attention to the multi-interface linkage between immune cells. This conceptual proposal invites theoretical developments and quantitative analyses that lead to experimental test. Even on a phenomenological level, a number of factors may prove important to consider. First, in this study the ceiling is estimated based on equilibrium binding constants where pulling forces cause a small change. Given that the tug-of-war setting of antigen extraction implements a comparison of binding affinities via kinetic rates, it might be fruitful to describe the non-equilibrium process of bond rupture in which tugging forces can modulate the effective bond strengths, potentially altering the range of distinguishable affinities. Second, the stiffness of antigen-presenting cells is found to influence how strongly B cells pull on the BCR-antigen interaction. A predictive theory of affinity discrimination must capture this mechanosensing behavior. Third, coupling may result from membrane-mediated interactions or sharing of the cytoskeletal load. Last but not least, alternative sources of constraints on maximum antibody affinity evolvable in vivo, downstream of antigen acquisition, warrant further investigations and may well reveal an unexpected evolutionary underpinning for these limits.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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