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B cell receptors and free antibodies have different antigen-binding kinetics

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Abstract-

Since the pioneering works of Berg and Purcell, discriminating between diffusion followed by binding has played a central role in understanding cell signaling. B cell receptors (BCR) and antibodies (Ab) challenge that simplified view as binding to the antigen follows after a chain of diffusion and rotations, including whole molecule rotation and independent tilts and twists of their Fab arms due to their Y-shaped structure and flexibility. In this paper, we combine analytical calculations with Brownian simulations to derive the first-passage times due to these three rotations positioning the Fab paratopes at a proper distance and orientation required for antigen binding. Our results indicate that when measuring Ab–Ag effective kinetic binding rates, using experimental methods in which the analyte is in solution only gives values proportional to the intrinsic binding rates, k+, and k-, for values of k+ up to 109 s-1. Beyond that, a plateau of the effective 3D on rate between 108 M-1 s-1 and 109 M-1 s-1 is attained. Additionally, for BCR–Ag interactions, the effective 2D on and off binding rates can only be inferred from the corresponding effective 3D on and off rates for values of effective 3D on rates lower than 106 M-1 s-1. This is highly relevant when trying to relate BCR–antigen-binding strength and B cell response, especially during germinal center reactions. Therefore, there is a pressing need to reexamine our current understanding of the BCR–antigen kinetic rates in germinal centers using the latest experimental assays for BCR–Ag interactions.

Index Terms- B cell receptor; humoral response; immunoglobulins; first-passage times; kinetic rates

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